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The Lactic Acid Content of the Blood and the Partition of Inorganic Sulphate in the Serum of Patients With Hepatic Disease*

By E. G. Wakefield, M.D., *Fellow in Medicine, The Mayo Foundation, and* Carl H. Greene, M.D., *Division of Medicine, the Mayo Clinic, Rochester, Minnesota*

THE majority of tests for hepatic function in clinical use at the present time are concerned primarily with disturbances in the formation and excretion of bile.[11] Disturbances in the metabolic activity of the liver, on the other hand, are much less readily demonstrated in cases of hepatic disease. Significant disturbances in the level of blood sugar that can be ascribed solely to hepatic insufficiency, are exceedingly rare. Our experience with both fructose and galactose tolerance tests has indicated that although positive tests occur with greater frequency in the presence of hepatic disease, yet so many other factors influence the response to sugar tolerance tests, and the individual variations are so great, that such tests are of little diagnostic value in any individual patient.

Experimental work on animals has amply demonstrated the rôle of the liver in the catabolism of the amino acids and the formation of urea. The blood urea in cases of jaundice tends to fall within the lower limits of normal but is not sufficiently lowered, of itself, to be of diagnostic significance. Other factors besides hepatic insufficiency probably are responsible for this reduction in the blood urea. Certainly the occasional development of uremia in cases in which the liver is injured indicates that ureogenesis is still active.

Various other tests, among them the study of the level of lactic acid in the blood, and of the rate of disappearance from the blood of intravenously injected solutions of sodium lactate, have been suggested as tests for hepatic insufficiency. Several investigators, including Schumacher and Adler and Lange have reported that in cases of cholecystitis or cholelithiasis, or in cases of mild catarrhal jaundice, the concentration of lactic acid in the blood was normal, whereas, in cases of acute yellow atrophy, carcinoma with extensive metastasis to the liver, cholangitis, advanced cirrhosis, or in other types of marked hepatic disturbance, they found that the concentration of lactic acid in the blood was increased. Beckmann, and Beckmann and Mirsalis, on the other hand, con-

*Submitted for publication September 6, 1929.

sidered that although there was an elevation of the amount of lactic acid in the blood in some cases of hepatic disease, such increases did not occur with sufficient frequency and were not sufficiently marked to be of great diagnostic significance. They emphasized, instead, the value of tolerance tests in which a solution of sodium lactate was injected intravenously and its rate of disappearance from the blood determined. In cases of hepatic disease, there was retention of injected lactic acid, which they considered of clinical significance. Similar results were reported by Adler and Lange, Schumacher, and Perger. The last two, in particular, have pointed out the significance of circulatory disturbances or of changes in the synthesizing activity of the musculature as additional factors in determining the rate of disappearance from the blood of injected lactic acid.

The liver is assumed to be active in the detoxification of various phenolic compounds absorbed from the intestine which are then conjugated and excreted in the urine as glycuronates or ethereal sulphates. Various proposed tests of hepatic function have been based on the administration of such materials as thymol, camphor or salicylic acid,[1, 9, 12, 13] and the demonstration either of glycuronates or of an increase in the ethereal sulphates in the urine. Such tests, however, have not been of proved clinical value. Pelkan and Whipple administered phenols to dogs and noted that the proportion of conjugated phenol in the blood was decreased after experimental injury to the liver. Such a test is not applicable clinically; however, Denis, and Wakefield recently have demonstrated the presence of ethereal sulphates in the blood of normal individuals. The ethereal sulphates in the blood, therefore, afford a possible index to conjugation or detoxification by the organism.

We have studied the content of the blood in lactic acid and the partition of sulphate in the serum, in a series of twenty-six patients who were in hospital suffering from hepatic disease of varying severity. The majority of them were given diets containing 50 gm. of protein, 80 gm. of fat and 350 gm. of carbohydrate and furnishing 2,400 to 2,500 calories daily. The intake of fluid was liberal except in the cases with cirrhosis and ascites. In these, the intake of fluid was limited to 800 c.c. daily.

All analyses were made of blood drawn in the morning, before breakfast. The lactic acid was determined by a modification of the method of Friedman, Cotonio and Shaffer. The partition of sulphate in the serum was determined by the method of Wakefield. The blood urea, the blood sugar and the serum bilirubin as well as the sulphates, are included in the accompanying table.

Comment

In the present series of cases, the content of lactic acid of the sample of blood taken before breakfast was 15 mg. or greater in nine, and 20 mg. or greater in six, of a total of twenty cases studied. In these, the level may be slightly, but by no means markedly, increased over the normal level. All the patients in whom the lactic acid

CHEMICAL CHANGES IN THE BLOOD IN HEPATIC DISEASES

								Sulphate partition in serum			
Case	Age	Sex	Serum bilirubin mg. for each 100 c.c.	van den Bergh direct reaction	Blood urea, mg. for each 100 c.c.	Blood sugar, mg. for each 100 c.c.	Lactic acid, mg. for each 100 c.c.	Total sulphates, mg. for each 100 c.c.	Inorganic sulphates, mg. for each 100 c.c.	Conjugated sulphates, mg. for each 100 c.c.	Diagnosis
1	50	M	1.2	+	24	76	9.0	7.5	4.5	3.0	Myocardial failure; chronic passive congestion of liver
2	62	M	0.8	+	21	91	9.8	4.2	3.0	1.2	Cholecystitis with stones
3	31	M	1.5	+.	23	100		6.6	3.7	2.9	Cholecystitis
4	52	M	0.7	0	21	119	7.9	5.7	4.2	1.5	Cholecystitis
5	42	M	1.3	+	31	82	11.3	9.9	6.2	3.7	Stone in common bile duct
6	56	M	4.3	+	16	93		6.0	3.6	2.4	Cholecystitis with stones; obstructive jaundice
7	52	M	14.0	+	21	83	9.0	3.6	1.6	3.0	Obstructive jaundice; stone in common bile duct
8	28	M	4.1	+	37	110	16.7	9.0	6.0	3.0	Obstructive jaundice; stone in common bile duct
9	45	M	10.4	+	25	94	15.3	4.8	3.0	1.8	Stone in common bile duct
10	61	M	5.2	+	21	85	8.1	7.3	7.2	0.1	Obstructive jaundice, stones in common bile duct; severe hepatitis
11	63	M	23.4	+	19	100	17.0	7.5	3.9	3.4	Obstructive jaundice; stricture of common bile duct
12	38	M	4.1	0	21	90	12.0	7.2	5.1	2.1	Obstructive jaundice; stricture of common bile duct
13	52	F	5.4	+	22	78	22.1	3.0	3.0	0.0	Obstructive jaundice; stricture of common bile duct following operation (elsewhere)
14	44	M	19.6	+	19	72	9.3	6.0	6.0	0.0	Obstructive jaundice due to injury to common bile duct at operation (elsewhere)
15	41	F	4.4	+	12	85	20.0	3.4	3.4	0.0	Obstructive jaundice; stricture of common bile duct*

*Patient died; diagnosis confirmed at necropsy.

CHEMICAL CHANGES IN THE BLOOD IN HEPATIC DISEASES (Continued)

								Sulphate partition in serum			
Case	Age	Sex	Serum bilirubin mg. for each 100 c.c.	van den Bergh direct reaction	Blood urea, mg. for each 100 c.c.	Blood sugar, mg. for each 100 c.c.	Lactic acid, mg. for each 100 c.c.	Total sulphates, mg. for each 100 c.c.	Inorganic sulphates, mg. for each 100 c.c.	Conjugated sulphates, mg. for each 100 c.c.	Diagnosis
16	42	M	12.3	+	19	114	11.0	4.8	3.7	1.1	Obstructive jaundice; neoplasm of pancreas
17	38	M	23.0	+	20	100		6.0	3.3	2.7	Obstructive jaundice; neoplasm of pancreas
18	38	M	18.0	+	13	111	7.7	7.6	6.5	1.1	Intrahepatic jaundice
19	54	M	23.2	+	10	93	13.2	3.0	6.0	3.0	Intrahepatic jaundice
20	43	M	24.4	+	20	83	20.1	6.4	6.0	0.4	Subacute hepatitis with jaundice
21	68	M	4.4	+	16	83	20.0	1.5	1.3	0.2	Subacute hepatitis with jaundice
22	69	M	18.5	+	18	154	7.1	3.7	3.7	0.0	Biliary cirrhosis of liver; chronic cholecystitis with stones*
23	52	M	3.8	+	18	90	20.5	3.2	3.0	0.2	Portal cirrhosis of liver
24	15	F	1.2	0	40			8.2	8.0	0.2	Portal cirrhosis of liver*
25	60	F	6.0	0	20			6.0	6.0	0.0	Portal cirrhosis of liver*
26	53	M	27.2	+	133	100	26.5	6.0	6.0	0.0	Hemangioma of the liver*

*Patient died. Confirmed at autopsy.

content of the blood was increased were in a serious condition; yet there were others, such as the patient represented by case 22, who presented the characteristic clinical picture of hepatic insufficiency and in whom the lactic acid content of the blood was normal. There was no definite correlation between the lactic acid and either the level of blood sugar or the serum bilirubin. Although the increase in the lactic acid is of interest from a physiologic point of view yet the changes were not sufficiently marked and did not occur with sufficient frequency to make the test of great diagnostic value in any individual case. This is especially true when one considers the various other factors which influence the concentration of lactic acid in the

blood. Thus, Campbell and Maltby found as great, or greater, increases during the course of fructose tolerance tests, and Meakins and Long reported much more marked changes in cases of circulatory failure. The increases after muscular exercise also emphasize the rôle of the muscles both in the production of lactic acid and its possible resynthesis to glycogen.

These same factors enter into the interpretation of tolerance tests based on the injection of solutions of sodium lactate. Furthermore, the latter is available commercially only as the racemic salt. Cori and Cori, in particular, have shown that whereas the injection of solution of sodium d-lactate leads to the formation of glycogen in the liver, its optical isomere, sodium l-lactate, forms hardly any hepatic glycogen. The racemic salt, therefore, is obviously unsuitable for use in the testing of hepatic function.

The inorganic sulphate in the serum was slightly increased in nearly 80 per cent of this series of cases, and was greater than 4.0 mg. for each 100 c.c. in thirteen cases of the twenty-six studied. Wakefield has pointed out the variability in the concentration of sulphate in the serum. He found that the values obtained in patients in hospitals who were without apparent renal or hepatic disease were higher than those found in active young normal adults. He also found that the concentration of sulphate in the serum was slightly affected by variations in the urinary output. The intake of fluid apparently was adequate in the present series of cases, and with one exception, case 22, there was no definite renal insufficiency. Many authors, however, such as Walters and Parham, have emphasized the development of renal insufficiency in jaundice, especially in the terminal stages, and the increase in the content of sulphate in the serum in these cases may be evidence of such renal injury.

The most striking change in the partition of sulphate in the serum in this series of cases was the reduction in the ethereal or conjugated sulphate fraction. The quantity of conjugated sulphates in the serum was 0.5 mg. for each 100 c.c. or less, in eleven of the twenty-six cases studied. All the patients with low values were seriously sick, and minimal values were found in the patients who died from hepatic insufficiency.

It is generally accepted that the ethereal sulphate[14] fraction in the urine varies with the amount of intestinal putrefaction. Dietary influences also play a part, for a diet of meat increases, and a diet of carbohydrate decreases, the output. If the level of ethereal sulphate in the blood varies in the same manner as the urinary output, the changes observed may be ascribed either to the special diet of these patients or to the effect of biliary obstruction and the resultant exclusion of bile from the intestine. Biernacki, on the other hand, has described an increase in the excretion of ethereal sulphate in the urine in cases of jaundice. The changes in the level of ethereal sulphate of the serum in this series of cases cannot be wholly explained on this basis, however, for they are apparently more closely related to the severity of the hepatic disease than they are to the presence or absence of biliary obstruction. Although this re-

lationship is very suggestive, yet too little is known regarding the relationship between the physiologic activities of the liver and metabolism of sulphur to permit the dogmatic statement that this reduction in the level of ethereal sulphate in the blood is an index of hepatic insufficiency.

Summary

A slight increase in the content of lactic acid of samples of blood taken before breakfast was found in some patients with severe hepatic disease. The increase was not sufficiently great, and did not occur with sufficient frequency, to make this test of great diagnostic significance or usefulness.

The inorganic sulphates in the serum were increased slightly in the present group of cases, whereas the conjugated or ethereal sulphates were reduced to less than 0.5 mg. for each 100 c.c. of serum in patients with severe or terminal hepatic disease. Further study is necessary to determine the diagnostic and prognostic value of this observation.

BIBLIOGRAPHY

[1]Adler, A. and Lange, H.: Der Milchsäuregehalt des Blutes bei Leberkrankheiten. Deutsch. Arch. f. klin. Med., 1927, clvii, 129-142.

[2]Beckmann, K.: Resynthese der Milchsäure bei Störungen der Leberfunktion. Klin. Wchnschr., 1927, vi, 2229-2231.

[3]Beckmann, K.: Klinische Erfahrungen mit der Leberfunktionsprüfung durch Milchsäurebelastung. Ztschr. f. klin. Med., 1929, cx, 163.

[4]Beckmann, K. and Mirsalis, T.: Der Milchsäuregehalt des Blutes nach Milchsäureinjektion bei experimentellen Leberschadigungen. Deutsch. Arch. f. klin. Med., 1928, clix, 129-146.

[5]Biernacki, E.: Ueber die Darmfäulniss bei Nierenentzündung und Icterus nebst Bemerkungen über die normale Darmfäulniss. Deutsch. Arch. f. klin. Med., 1891, xlix, 87-122.

[6]Campbell, W. R. and Maltby, E. J.: On the significance of respiratory quotients after administration of certain carbohydrates. Jour. Clin. Investigation, 1928, vi, 303-317.

[7]Cori, C. F. and Cori, G. T.: Glycogen formation in the liver from d- and l-lactic acid. Jour. Biol. Chem., 1929, lxxxi, 389-403.

[8]Denis, W. and Reed, Lucille: Methods for the determination of some of the nonprotein sulfur compounds of blood. Jour. Biol. Chem., 1926-1927, lxxi, 191-208.

[9]Foster, C. S. and Kahn, Max: A study of the tests of liver functions. Jour. Lab. and Clin. Med., 1916-1917, ii, 25-36.

[10]Friedemann, T. E., Cotonio, Margherita and Shaffer, P. A.: The determination of lactic acid. Jour. Biol. Chem., 1927, lxxiii, 335-358.

[11]Greene, C. H., Snell, A. M. and Walters, Waltman: Diseases of the liver. I. A survey of tests for hepatic function. Arch. Int. Med., 1925, xxxvi, 248-291.

[12]Händel, Marcel: Klinisch experimentelle Studien über die entgiftende Funktion der Leber. I. Über Schwefelsaure-und Glykuronsäurepaarung bei Leberkranken. Ztschr. f. d. ges. exp. Med., 1924, xlii, 172-193.

[13]Kahn, Max: Sulphoconjugation as a test of liver function. Am. Jour. Med. Sc., 1918, clv, 668-672.

[14]Kahn, Max and Goodridge, F. A.: Sulfur metabolism. A review of the literature. Philadelphia, Lea and Febiger, 1926, xiv, 17-831 pp.

[15]Meakins, Jonathan and Long, C. N. H.: Oxygen consumption, oxygen debt and lactic acid in circulatory failure.

Jour. Clin. Investigation, 1927, iv, 273-293.

[16]Pelkan, K. F. and Whipple, G. H.: Studies of liver function. III. Phenol conjugation as influenced by liver injury and insufficiency. Jour. Biol. Chem., 1922, I, 513-526.

[17]Perger, Hans: Über die Resynthese der Milchsäure bei Kreislaufkranken. Klin. Wchnschr., 1927, vi, 1324-1326.

[18]Schumacher, Hertha: Untersuchungen über den Milchsäuregehalt des Blutes bei Karzinomkranken. Klin. Wchnschr., 1926, v. 497-499.

[19]Schumacher, Hertha: Das verhalten der Blutmilchsäure bei Leberkranken. Klin. Wchnschr., 1928, vii, 1733-1737.

[20]Wakefield, E. G.: The colorimetric determination of total and inorganic sulfates in blood serum, urine and other body fluids. Jour. Biol. Chem., 1929, lxxxi, 713-721.

[21]Wakefield, E. G.: Inorganic serum sulphates in renal insufficiency: a comparative study of blood urea and creatinine. The effect of diuresis on serum sulphates. Arch. Int. Med., 1929, xliv, 244-251.

[22]Walters, Waltman and Parham, Duncan: Renal and hepatic insufficiency in obstructive jaundice. Surg., Gynec., and Obst., 1922, xxxv, 605-609.

Spontaneous Rupture of the Heart; Perforation of the Interventricular Septum*†

By Albert S. Hyman, M.D., *New York*

RUPTURE of the heart is always of serious moment; death is said to follow almost instantaneously. This is especially true of the so-called "spontaneous ruptures" of the heart where the underlying pathology has in most cases been due to a previous disturbance in the circulation of the coronary vessels.

Ruptures of the heart as a result of trauma, gunshot, or penetrating wounds are, however, not necessarily fatal. I have reported the instance of a young negro who was able to run nearly a quarter of a mile with a knife blade sticking through his chest and piercing the left ventricle.[1] Repeated cardiovascular examinations of this patient during the past four years have shown him to be in excellent physical condition and without cardiac symptoms. Other observers have reported similar experiences; Vaughan,[2] Constantini,[3] and Hesse[4] have collected many such cases from the literature.

The military surgeons have developed an extensive literature upon injuries to the heart by piercing instruments. If operated upon soon enough and before much hemorrhage has occurred, most such perforations of the heart do well and convalescence is prompt.

Rupture of the heart as the result of cardiovascular pathology is, however, almost always fatal. The explanation of the end-results of these two types of cardiac injuries lies perhaps in the fact that in the traumatic group the cardiovascular system is usually normal and unless the damage to the heart be excessive there is sufficient myocardial reserve power to maintain an adequate circulation. In the pathologic group, on the other hand, the rupture has occurred because of widespread myocardial involvement which has reduced the cardiac reserve to a hazardously low level; an adequate circulation under these conditions is thus impossible and death occurs.

The pathology underlying spontaneous rupture of the heart is apparently vascular in origin. Disturbance and interference with the coronary circulation quickly leads to under nourishment of the myocardium with an accompanying loss in functional ability. Such disturbances arise from sclerosis

*From the Witkin Foundation for the Study and Prevention of Heart Disease, Beth David Hospital, New York City.

†Read in a Symposium on Heart Disease at the Metropolitan Medical Society, New York, Jan. 22, 1929.

and gradual stenosing of the coronary arterial tree. Where the process is equally distributed throughout the entire heart there may be no or very little manifestation of the condition and when found in the fifth and sixth decades may, with some justice, be considered as a normal phase of senescence.

Where, however, the sclerosing process appears unequally distributed in the coronary system, a sudden narrowing or complete occlusion of an artery may lead to prompt infarction of the area supplied by the affected vessel. The usual pathologic changes now take place as elsewhere in the body whenever an end-artery fails to carry blood to its part. In the heart, the ischemic area of infarction may become congested from venous back flow; there is extravasation of blood cells and a rapid destruction of collagen and later, of the myocardial fibers themselves.

If the infarcted area be of limited extent, the normal reparative process ends in fibrosis and scarring of the heart muscle; but when larger portions of the myocardium are involved, liquefaction necrosis occurs and a sterile abscess of the heart develops. The hazard of such an area of necrosis depends apparently not so much upon its size as upon its location. If it lies within the so-called "pressure zones" of the heart, danger of rupture may be very great. When it occurs in or near the conducting pathways of the heart, various disturbances of rhythm may occur and when it develops in the "silent areas" of the heart there may be no evidence of its presence. The healing process may be active enough to absorb certain small areas of necrosis and the resulting scar when subjected to pressure may gradually stretch and lead to aneurysmal dilatations of the heart wall.

Rupture of infarcted areas in the wall of one of the cardiac chambers is followed by immediate hemorrhage into the pericardium.[5, 6, 7] Instantaneous death usually occurs but the patient may go into profound shock and die a few hours later.[8, 9] Few cases have lived longer than twenty-four hours.[10, 11]

The cause of sudden death in these cases is apparently not well understood; hemorrhage into the pericardium itself is not sufficient to produce such extreme shock and death. As noted before, perforation of the heart by foreign bodies is not accompanied by this clinical picture. Moreover, the actual loss of blood in spontaneously ruptured hearts may be very small; in one case only 5 c.c. was found. In other cases from 50 to 200 c.c. were discovered.

The capacity of the normal pericardium is not great; experimentally in the cadaver, only 200 to 350 c.c. of fluid can be injected. Ordinarily the pericardium does not stretch quickly and while it is true that as much as 1,000 c.c. have been removed not infrequently in cases of hydropericardium, the capacity of the pericardium in this latter condition has been slowly and gradually extended.[12]

Hemorrhage into the pericardium cannot of itself be the explanation of the sudden death which occurs in spontaneously ruptured hearts. Other

factors, not the least of which is the associated pathology in the heart, must be considered. It has been previously indicated that when the myocardial reserve has not been lowered by undernourishment or disease, extensive damage may be sustained by the heart without loss of adequate circulation. Where, however, the myocardial reserve is low any sudden additional damage, be it ever so slight, may be sufficient to over-burden the circulation and cause shock and death.

Erdheim has repeatedly demonstrated spontaneous ruptures of either ventricle which barely admit the tip of a probe. On the other hand, large infarcted areas have been discovered in the walls of the ventricles in patients dying from extracardiovascular diseases.

These apparently paradoxical post mortem findings may be explained by assuming that the perforation regardless of its size is accompanied by unusual electrodynamic phenomena which cause a damaged myocardium to develop an ectopic rhythm and which may precipitate an attack of ventricular fibrillation with immediate death.

Mention has been made that where the sclerosing process has been unequally distributed throughout the coronary tree, the danger from infarction and its sequelae is greater than in the heart where the arterial degenerative process is more widespread. This fact corresponds very closely to the clinical observation that coronary artery sclerosis is more dangerous when it occurs in the fourth and fifth decades than in the sixth and seventh. The senescent heart is apparently better adapted to the new pathology than is the younger, more irregularly damaged cardiovascular system.

In addition to this type of the sclerosing process, syphilis of the cardiovascular system may produce a somewhat similar type of pathology. More often the luetic infection affects only the orifices of the coronary arteries and the patient exhibits the stenocardial syndrome; sudden death in such cases is usually due to occlusion of an entire coronary vessel in contrast to the other types of vascular degenerative change which pick out smaller subdivisions of the coronary tree.

The clinical picture of spontaneous rupture of the heart is not characteristic; the symptomology may be and frequently is referred to the gastro-intestinal tract. The patient complains of severe abdominal pain which is not readily localizable. He is nauseated and vomits; he rapidly goes into shock with cold cyanosed extremities and a livid pallor is noted. The pulse is rapid and often impalpable. The clinical picture may suggest in every way a ruptured gastric or duodenal ulcer. Symptoms may be referrable to the chest, the patient complaining of terrific pain in the lower back or the axillae. The pain may be referred upward into the neck. Strangely enough, the precordial region may be entirely free from any pain or symptom. Extreme and rapid prostration is, however, a most constant finding. Death may occur promptly; in those cases where a diagnosis of ruptured ulcer has been made the patient may die upon the operating table, the sur-

geon being unfairly credited for the death.

Auscultation of the heart is usually quite unsatisfactory; because of the patient's noisy respiration no heart sounds are audible. On close attention, the basal heart sounds can be identified but rarely can the apical sounds be heard. Of unusual interest is the occurrence of a peculiar harsh and shrill murmur which is systolic in time; this murmur appears very close to the ear and its loudness is out of proportion to the character and intensity of the other heart sounds. I believe this murmur to be of great importance in the diagnosis of spontaneour rupture of the heart; it is not mentioned in the available literature but it has been noted six times in cases which subsequently have come to post mortem and in which pathologic perforations have been found. The peculiar quality of this murmur in conjunction with other cardiovascular findings is not readily forgotten once the clinician has discovered it.

While spontaneous rupture of the heart into the pericardium is not especially uncommon, rupture and perforation of the interventricular septum is apparently infrequent. Vaquez[13] mentions the possibility of septal rupture in acute tricuspid valvular infections; Cabot[14] describes an infarction and aneurysmal dilatation of the heart with involvement of the interventricular septum. Direct perforation of the septum alone has not been found in the literature. The following case is therefore of interest in that the diagnosis was suggested and made prior to death and the post mortem examination.

H. S., a man, age 52, was admitted to the Cardiac Service of the Beth David Hospital, October 29, 19928 (Hospital No. 28-2658), at 11:30 A.M., about one hour after I had seen him in consultation through the courtesy of the family physician, Dr. Joseph Nisonoff. The patient's history was typical and is here related in some detail. He had previously enjoyed good health and was of rugged constitution. He had been awakened suddenly that morning with a severe cramp-like pain in the lower abdomen; he felt nauseated and vomited several times. The pain then became localized in the epigastric region and reached such an intensity that the patient rapidly became prostrated.

The family physician being unavailable, an emergency ambulance was called and the ambulance surgeon made a diagnosis of ruptured duodenal ulcer; he suggested immediate hospitalization and operation. The relatives objected on the ground that the patient had never had any previous gastro-intestinal symptoms. Two hours later the family physician arrived and he noted the patient's desperate condition and the very feeble heart action. He graciously suggested that I see the case and I reached the patient about four hours after the onset of the original attack of pain.

The patient was now in extreme shock, with cold clammy perspiration, deeply cyanosed and breathing with noisy respirations. There was no palpable pulse at the wrist; the superficial area of cardiac dullness appeared widened to percussion. No heart sounds were heard at the apex but the basal sounds were rapid (about 130) and of very poor quality. Unusual and striking was a very shrill systolic murmur which was heard equally well over the entire precordium. The peculiarities of this murmur have been described before. I made a diagnosis of spontaneous rupture of the heart and advised immediate hospitalization.

Directly upon admission to the hospital the patient was taken to the Heart Station where electrocardiographic studies were made. He was then quickly removed to his room and intravenous glucose and metaphyllin were ordered. At this time a member of the Interne Staff called attention to

the fact that the heart sounds were now more audible at the apex as well as at the base but the shrill superficial character of the murmur remained unchanged.

In commenting upon this I suggested that we might be concerned here with a rare phenomenon—an interventricular perforation. Assuming that the obscuring of the heart sounds could be due to two factors: (1) The blood in the pericardium acting to dampen the sound waves in exactly the same manner as fluid does in pericarditis, and (2) the loss of tone of the heart muscle as a result of the terrific injury it had undergone; with the return of the latter no change in the intensity of the heart sounds would be evident unless the quantity of blood in the pericardium be very small. The loud, shrill systolic murmur suggested a large perforation and if there was no or little blood in the pericardium, the rupture must be between two cardiac chambers, possibly in the interventricular septum.

The patient's condition at this time was so desperate that only emergency measures could be employed and he died about one-half an hour later. From the initial attack of pain to death was about five and a half hours.

The electrocardiographic studies (Fig. 1) are of interest; characteristic T-wave alterations are noted especially well in Leads I and II. There was no axial deviation of the heart nor was there any delay in the QRS-complex. Simultaneous polygraphic tracings of the brachial artery taken with each of the three leads was normal. The rate was about 100 beats per minute and there was a normal sino-auricular rhythm.

This study points out clearly the value of electrocardiographic investigation in acute cardiac conditions. Experience has shown that there may be a considerable delay between the occurrence of cardiac damage and its manifestation by electrocardiographic examination; several days or even weeks may be required before the characteristic changes found in the initial ventricular complex make their appearance.[15]

Discovery of T-wave alterations in this case suggest that the patient has had disturbances of his coronary circulation for some time but these changes have all taken place prior to the accident which led to death. On the other hand long standing areas of infarction when they occur in regions near the septum usually give unmistakable signs in the electrocardiogram: widening of the QRS-complex, splitting and feathering of the R-wave and bundle branch block are the usual changes that are found.

Post mortem examination was performed by the hospital Pathologist, Dr. J. Geiger. The pericardium was opened and found *free from blood*. The heart was slightly enlarged and weighed 310 grams. When it was opened a recent perforation large enough to admit one finger was discovered in the interventricular septum near the apex. (Figure 2) Both coronary arteries were found to have irregular patches of sclerosis; the right was more involved than the left. In the terminal subdivision of the anterior descending branch of the right coronary artery was found a rather large thrombus which had apparently broken off from an adjacent area. The portion of the heart supplied by this vessel was pale and thinned out and appeared to be not very recent. In the apical part of the heart especially in the right ventricle was a large hemorrhagic area which was torn through

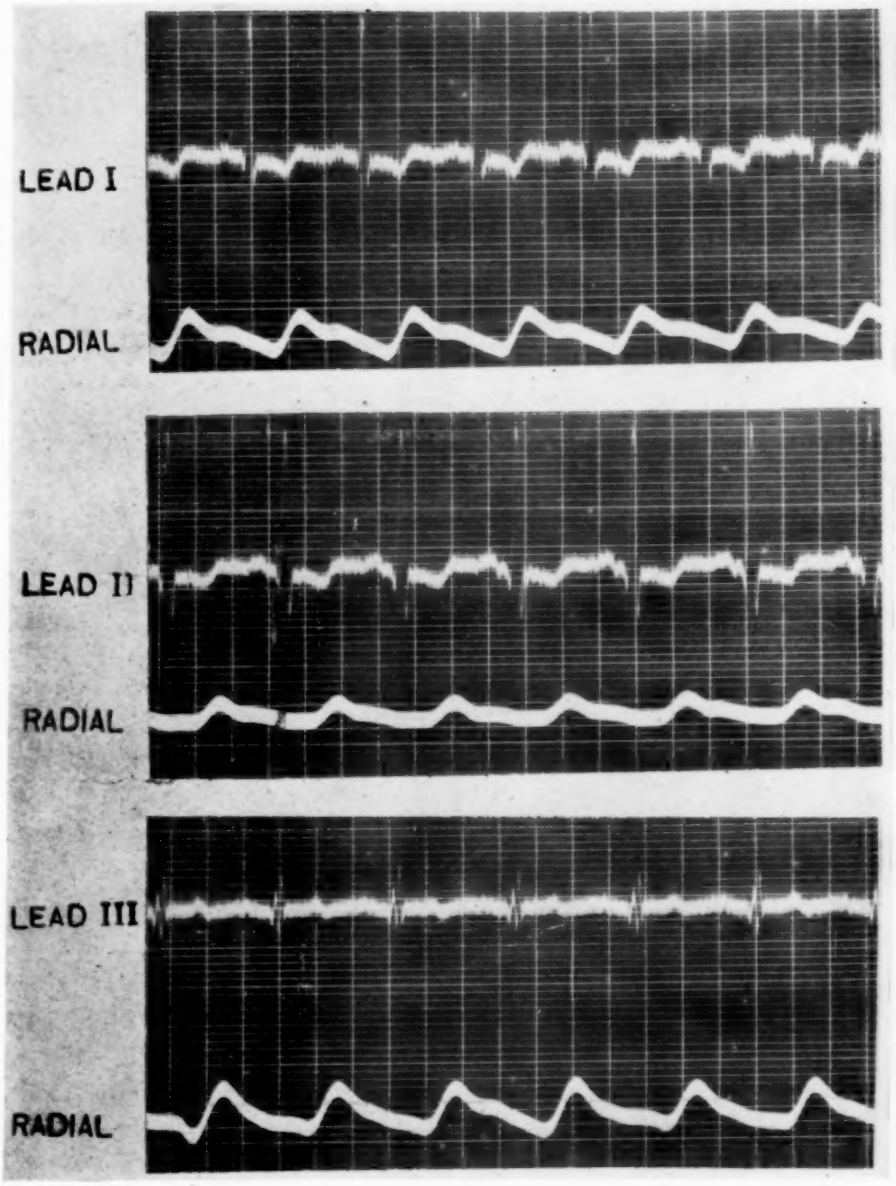

FIG. 1. Electrocardiographic and polygraphic studies made about one-half hour before death; with the exception of the T-wave alteration the records do not suggest the widespread damage which is present in the heart. This is a common finding in recent injuries to the heart.

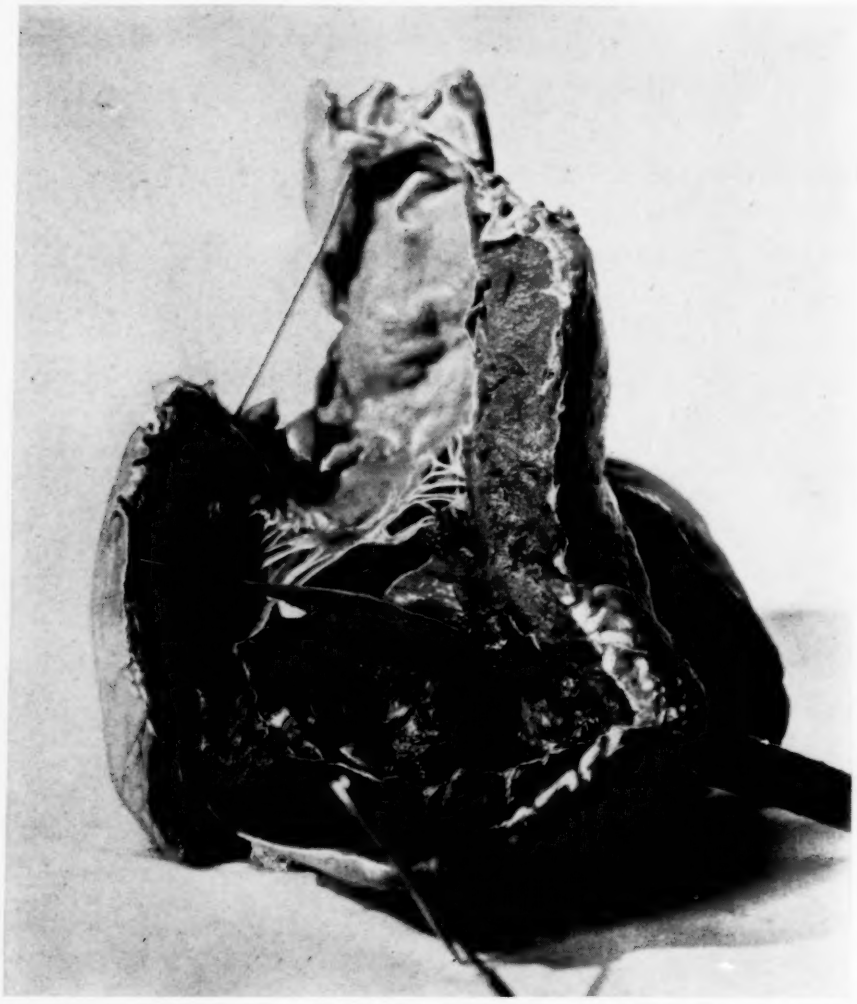

FIG. 2. Photograph of heart seen from the left; the left ventricle is exposed. A flat wooden probe (x—x′) is passed through the perforation at the bottom of the interventricular septum near the apex of the heart.

as it approached the septum. Several mural thrombi were found in the left ventricle. The valve mechanism was normal. The aorta was not enlarged but showed many atheromatous plaques.

SUMMARY

Spontaneous rupture of the heart is not an infrequent condition; it should be suspected in all patients of middle age or older who present the clinical picture of sudden collapse and rapid prostration. The close resemblance to the symptomatology presented by ruptured gastric or duodenal ulcer can not be over emphasized; the extreme vasomotor collapse should put the surgeon on his guard. Discovery of a shrill

superficial murmur, systolic in time, which is out of proportion to the quality and character of the other heart sounds, should call to mind the possibility of spontaneous rupture of the heart.

Hemopericardium always accompanies spontaneous rupture of the heart to a greater or lesser degree, but the amount of blood in the pericardium apparently bears no relation to the cardiovascular reaction to the injury. Prognosis is usually fatal in contradistinction to heart injuries as the result of trauma.

In the case presented, the rupture was between two cardiac chambers instead of into the pericardium; while this condition must be extremely rare, the outlook and pathology is the same. To those interested in deductive diagnosis, rupture of the interventricular septum presents a fertile field for speculative investigation.

REFERENCES

[1]Hyman, Albert S. and Fisher, J. L.: Posttraumatic Disturbances of the Heart, Am. Heart Journ., 1926, ii, 61.

[2]Vaughan, G. T.: Suture of Wounds of Heart, J. A. M. A., 1909, lii, 429.

[3]Constantini, H.: Surgical Treatment of Heart Wounds, Jour. de Chir., 1920, xvi, 383.

[4]Hesse, E.: End Results of Heart Suture, Policlinico, Rome, 1925, xxxii, 699.

[5]Buckley, R. C.: Spontaneous Rupture of Heart, Am. Journ. Path., 1928, iv, 249.

[6]Locke, E. A.: Five Cases of Spontaneous Rupture of Heart, Boston M. & S. Journ., 1927, cxcvii, 955.

[7]Miller, J.: Spontaneous Rupture of Heart, Canad. M. A. J., 1928, xix, 74.

[8]Smiles, C. J. and Middleton, W. S.: Spontaneous Rupture of the Heart, Wisconsin M. J., 1928, xxvii, 497.

[9]Thomas, C. J. and Tattersall, S. R.: Two Cases of Spontaneous Rupture of the Heart, Brit. M. J., 1927, i, 1096.

[10]Davenport, A. B.: Spontaneous Rupture of Heart; Statistical Summary, Am. Journ. Med. Sci., 1928, clxxvi, 62.

[11]Hodge, B. L.: Spontaneous Rupture of Right Ventricle, Brit. Med. Journ., 1927, i, 1096.

[12]Hinton, J. W.: Indirect Injury to Heart by Needles and Similar Foreign Bodies, J. A. M. A., 1929, xciii, 266.

[13]Vaquez, Henri: Diseases of the Heart, Saunders, Philadelphia, 1924, 398.

[14]Cabot, R.: Facts on the Heart, Saunders, Philadelphia, 1926, 540.

[15]Parsonnet, A. E. and Hyman, Albert S.: Applied Electrocardiography, Macmillan, New York, 1929.

A Clinical Study of a Graphic Method of Recording Blood Pressure*

By Louis Faugeres Bishop, M.D. *and* Louis Faugeres Bishop, Jr., M.D.,
New York

HALES' demonstration in 1733 proved that the movement of the blood carried with it a necessary consequence, that of pressure. This was made known one hundred years after the discovery of the circulation of the blood by Harvey, but another hundred years elapsed before this fact was given serious consideration. In 1828 Poiseuille introduced the mercury manometer of U form by which he was able to study blood pressure within a circumscribed space. Coagulation was retarded by sodium bicarbonate, a method in use today. All this work paved the way to newer discoveries and in 1847 Ludwig made use of the "kymographion," the forerunner of all modern graphic methods of precision. This earliest instrument obtained a pressure tracing from an open artery through a recording manometer, the tracing being made upon a revolving cylinder. It, however, recorded only a mean blood pressure and very elaborate compensatory adjustments were needed to obtain correct readings.

The work of Ludwig, in physiology, with his kymographion, made itself felt as a stimulus in the field of clinical medicine. A large number of further steps led up to the development of clinically useful apparatus. Riva Rocci's invention of a cuff and bulb device was the outstanding achievement in this work.

The further addition of devices for automatic record of blood pressure has greatly enhanced this work. Jacquet invented the sphygmotonograph in which he used the stylet of a metal manometer, which communicates with the brachial cuff and records directly on the tracing. Metal manometers, however, require standardization. An instrument, devised by Bingel, records every pressure change of 10 mm. by the interruption of an electic current. Another sphygmomanometer, that of Gibson, consists of a mercury manometer, with a double U-shaped tube. In the reading the abscissa must be doubled. The height of the mercurial column is automatically recorded, thus avoiding the personal equation. The instrument is accurate, but somewhat bulky. C. Singer has devised a very similar mechanism. Erlanger's apparatus is more suitable for laboratory than clinical use, on account of its complexity. Time and skill are needed to manipulate it, but the records are

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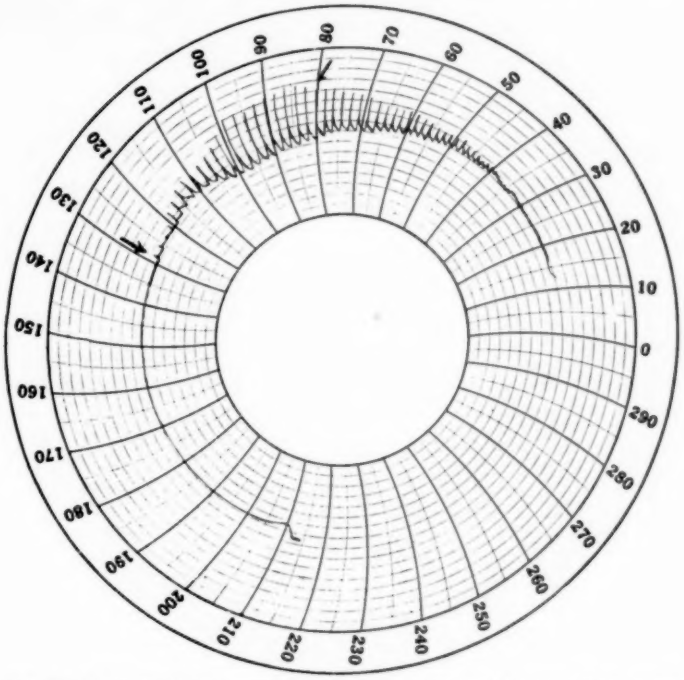
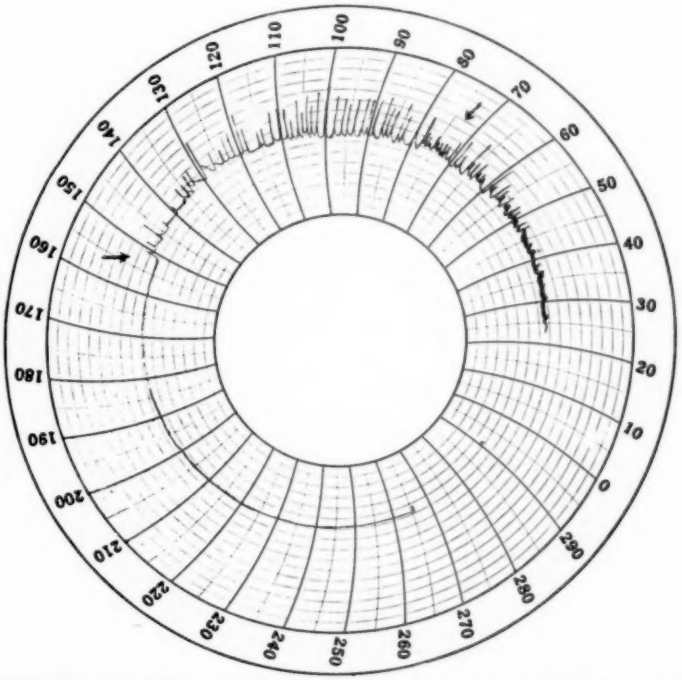


GRAPH I—Normal blood pressure curve taken with recording machine. Systolic 130—Diastolic 80.



GRAPH II—Blood pressure curve from case of auricular fibrillation. Complete irregularity in width and neight of waves. Systolic 130—Diastolic 75.

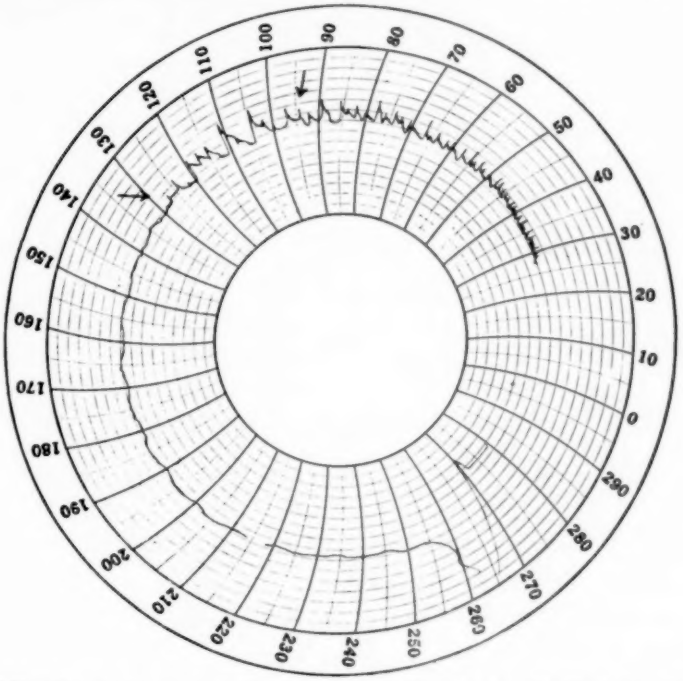
very accurate. Polygraphic attachments can be included and used for pulse tracings. The systolic readings come 5 mm. higher than the Riva Rocci, and the diastolic vary from 5 to 15 mm. The Uskoff sphygmotonograph, also, was devised for both blood pressure and pulse readings. It simultaneously records: (a) blood pressure in mm. Hg, (b) carotid pulse, (c) pulsation from brachial artery, (d) time in 1/5 second.

The graphic instrument of Silbermann is equipped with a radial and a brachial cuff, a mercury manometer, a float, a receiving drum for smoked paper and a registering device. The method of Brugsch consists of a U-shaped manometer and a revolving drum covered with white paper, ruled in cm. spaces. Muenzer has an elaborated and complicated instrument which he calls a sphygmoturgograph. The pulsations pass from the cuff through a balloon to the recording kymograph; the latter has two speeds, a slow one for blood pressure and a rapid one for pulse tracings.

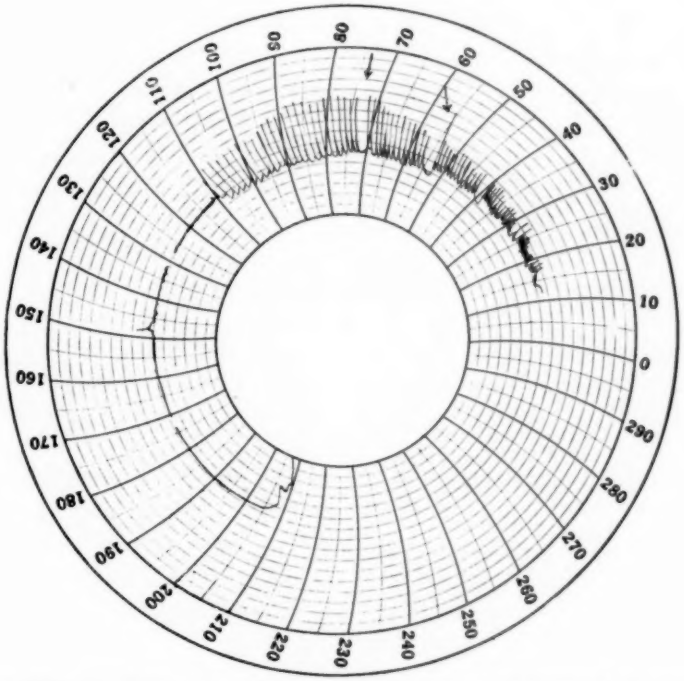
Fleicher's instrument is somewhat similar, but he uses a metal cylinder, containing a celluloid cylinder; the latter floats in a layer of oil. The air from the cuff imparts the pulsations to a counterweighted lever, thence by a wire to the recording needle. In an ingenious little instrument by Bussemius, another principle is used, that is, he eliminates driving force and simply lets a narrow upright supported strip of paper fall by gravity at a graduated rate past the pulsating tambour. The strip falls at 1 mm. per second. This device records both systolic and diastolic pressure. Another instrument, that of Wysbauw, is a modification of Erlanger, but has a double cuff which gives more accurate systolic readings.

Recently, Dr. L. A. Amblard of Paris, a pupil of Potain, has invented the "sphygmometoscope," a device for recording both systolic and diastolic pressure, also a pulse tracing. This device consists of an arm piece, a compression apparatus and a very sensitive manometer. A rigid leather band holds two cuffs, which can be inflated without touching. The inflating bulb has a stop cock, with a turning device on an index, a, b, or c. (a) is the inflation position; (b) the deflation; at (c) only the lower cuff communicates with the manometer. The machine has two speeds, viz.: one and three centimeters per second. A stylet can be moved over the face of the tambour at any part. The first abrupt increase in the tracing indicates maximal pressure; the first abrupt decrease equals minimal pressure.

In our study of graphic methods we have used the Tycos Recording Sphygmomanometer, one of the most recent on the market. The tracings are made directly on the revolving disk, and are purely pressure graphs caused directly by the arterial pulsations, and do not represent units of time or of time and pressure. No clock or motor is used, but instead, a small stream of air escaping from a light collapsible metal tube sets the kymograph in motion. Decrease of pressure of the cuff round the brachial artery causes deflation through the light tube. Diminishing pressure in the arm band allows the arterial force to be felt, and to be imparted to the



GRAPH III—Blood pressure curve from case of auricular fibrillation. Complete irregularity in width and height of waves. Electrocardiogram revealed an associated heart block. Systolic 125—Diastolic 95.



GRAPH IV—Blood pressure curve illustrating premature contraction occurring during the recording. Systolic 110—Diastolic 65.

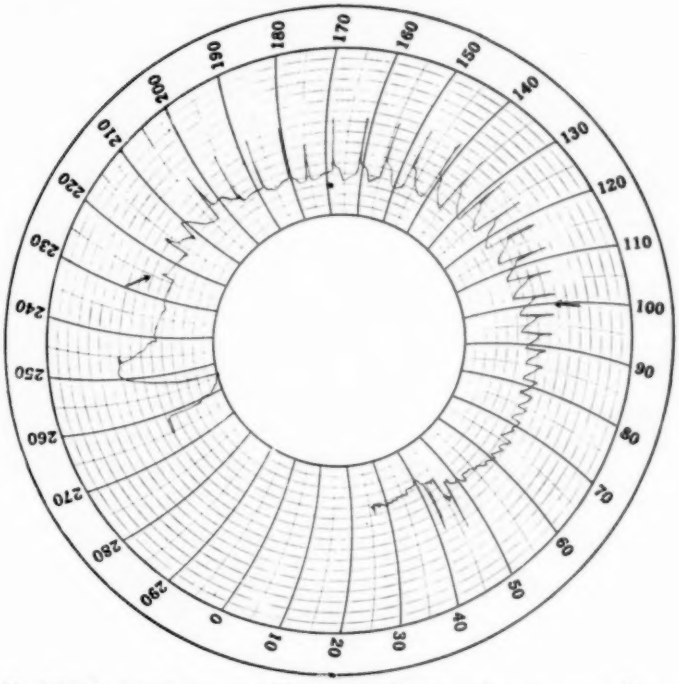
pen of the oscillometer, which in turn records the tracing on the moving disc.

A sleeve for the patient contains an upper and a lower cuff. The sleeve is fitted snugly to the arm just above the elbow and when inflated should just suppress the pulsation of the brachial artery. The sleeve adjusted, the patient is told to keep quiet and relaxed, and sufficient inflation having been secured, deflation is commenced by opening a valve. The puff of escaping air at once starts the disk revolving. The first impact to occur against the upper, or filter cuff, is the thud of the closed artery, which causes a slight pulsation—the so-called "hydraulic ram wave," which registers itself on the pointer and traces on the graph a series of short spikes directed inward toward the hub of the disc. As soon, however, as the surplus pressure of the cuff has been used up, that of the artery is released and begins to make itself felt. By this time the pressure of the upper cuff is lessening and allows the waves to pound upon the lower cuff. The effect of this is to set up a direct record, observable on the chart as a series of spikes pointed toward the periphery of the disc. What this really means is that systolic pressure is tracing its direct autograph on the diaphragm. Without manipulation this would naturally appear as a series of waves, but a method of so timing the rotation of the chart in relation to the oscillations of the pen has been worked out, so that, instead of waves, a series of spikes is produced and the *height of the spike*, which is an important feature, is brought into prominence.

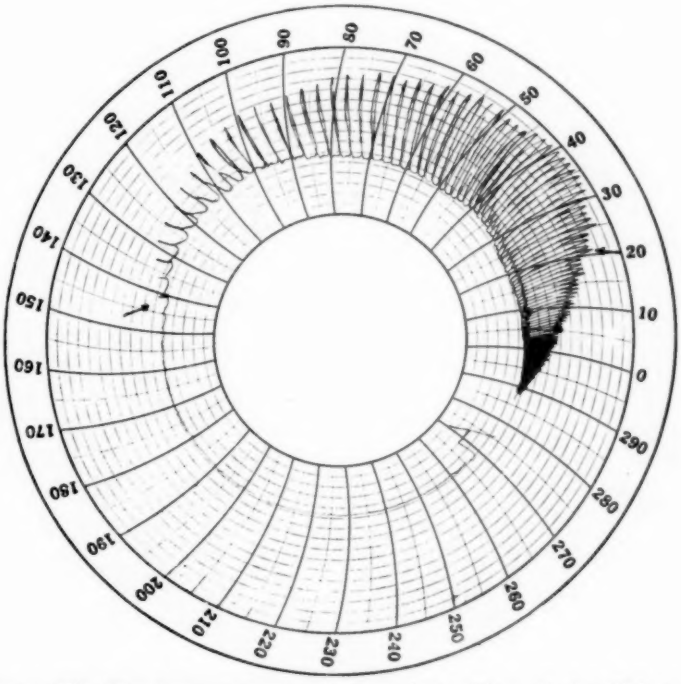
The first spike pointing toward the periphery traced bears relation to the first systolic sound. After the first spike the general character of the curve in this instrument is similar to that shown in other pressure instruments. The increase of pulsation in the released vessel under the cuff causes higher and higher spikes up to a certain point, at which they are seen to decrease in height and the peaks to become wider at the base. The first definitely shortened spikes and levelling corresponds to the phase of diastolic pressure and corresponds to the transaction of the third and fourth phase. We regard the first typical lowered and levelled spike as indicating diastole.

As has been said, the tracing is expressed in terms of pressure only. The chart is of disc shape and moves with angular motion, thus giving direct rates of speed to points of varying distance from the center. Second, the speed and the retardation are not uniform and these factors may be so adjusted as to bring out features in the tracing which it is desirable to emphasize and to lessen masking effects such as those produced by respiration.

The design of the cuff has been carefully worked out. According to von Recklinghausen, the narrower the cuff, the greater the pressure, and vice versa. The cuffs are standardized in such a way that the width affects pressure to the extent that the first spike on the tracing corresponds to the first sound, as heard in the normal individual by the normal ear. The listener's ear was standardized by the audiometer, and a subject was used in whom the sounds approached classic regularity.



GRAPH V—Blood pressure curve illustrating hypertension on recording machine. Systolic 225—Diastolic 100.



GRAPH VI—Blood pressure curve from patient with aortic insufficiency. Systolic 190—Diastolic 20.

During the past year we have used this graphic method in our office for the recording of about five hundred records in conjunction with our practice. We have carefully checked the reading thus made with the Becton-Dickinson manometer, and they have agreed very closely with our charts.

The few conclusions we would like to make are:

1. Removal of the personal equation in blood pressure is probably the most important point in the use of a graphic method.

2. Some conclusions can be drawn in regard to the cardiac arrhythmias from the records of blood pressure made with this instrument, but in no sense does it replace the electrocardiograph for this purpose.

3. The curves shown are purely graphs of blood pressure recording the pulsations of the brachial artery. They do not show any intracardiac manifestations.

4. In cases where ordinary methods are very difficult, as, for example, auricular fibrillation and paroxysmal tachycardia, the graphic method is of great value.

5. Should the future bring forth an instrument which was less complicated and did not require such skillful manipulation a great advance would be made in its clinical use.

BIBLIOGRAPHY

[1]Janeway, Theodore C., M.D.: The Clinical Study of Blood Pressure, D. Appleton & Co., 1904.

[2]Barr, Daniel R., M.D., Rochester, N.Y.: Preliminary Note on New Method of Recording Blood Pressure with Presentation of a Model, Anesth. & Analg., Dec., 1927.

[3]Morris, George Wm., A.B., M.D.: Blood Pressure, Lea & Febiger, 1917.

[4]Amblard, L. A., M.D.: Determination of Blood Pressure by Graphic Method: The Sphygmometrograph, J. de méd. de Paris, 26, 495, 1927.

Endogenous Obesity—A Misconception*

By L. H. Newburgh *and* Margaret Woodwell Johnston,
Ann Arbor, Michigan

THE physician who prescribes a low calorie diet to reduce the weight of his obese patients frequently deals with subjects who fail to lose weight during the period of observation. And the writers have satisfied their desire for an explanation of this seemingly paradoxical phenomenon by attributing it to abnormality of the endocrine glands—in particular the hypophysis, the thyroid, and the gonads. The logical conclusion to be reached from such a position is that these patients are the unfortunate victims of constitutional disease that unrelentingly causes a progressive deposition of adipose tissue, independent of activity or dietary habit. It is not to be expected that restriction in food will reduce the weight of such individuals. Those who support this hypothesis have placed themselves in a precarious position, since they are in fact denying the principle of the conservation of energy, and are disregarding the quantitative facts that form the foundation of our knowledge of energy transformations by man.

The sceptic who has not witnessed this apparent contraversion of natural law might be unwilling to admit its occurrence. But that is not the explanation. There can be no doubt about the fact that individuals sometimes maintain their weight while subsisting on very low calorie diets. Fig. No. 1 is a standard example of this phenomenon from our practice. After it had been demonstrated that 2300 calories maintained the weight of this obese young woman, the diet was abruptly reduced to 1500 calories. You note that this change caused an abrupt decline in weight lasting only two days. During the next eleven days the patient failed to lose weight in spite of the unquestionable caloric inadequacy of the diet. Furthermore, undernutrition diets may even be accompanied by gain in body weight, as Fig. No. 2 demonstrates. This patient gained three pounds in nineteen days, even though the diet was far below the requirement for maintenance.

The searcher after truth may question whether the patients, from whom such paradoxical weight records have been obtained, have not secured an extra supply of food without the knowledge of the attendants or whether the diet given the patient contained more energy (through an error) than was ordered. We have avoided these two sources of error by studying our

*Presented to the American College of Physicians, Boston, April 12, 1929.

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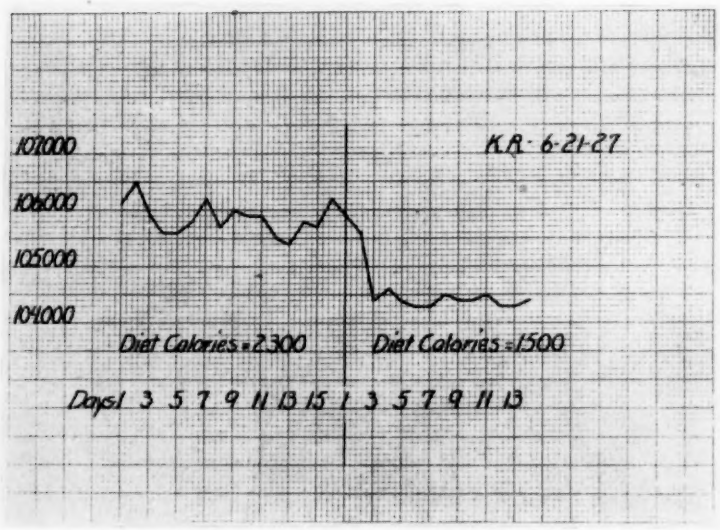


FIG. 1. An obese young woman maintains her weight, first on 2,300 calories and then on 1,500 calories.

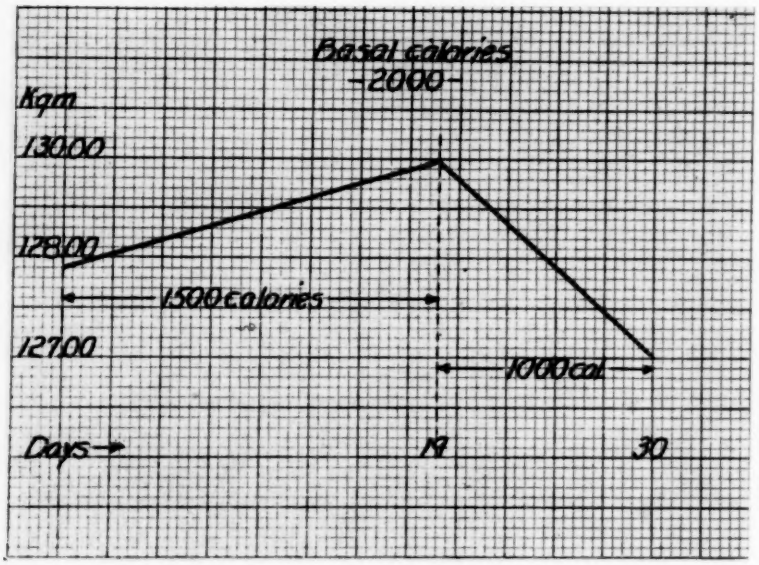


FIG. 2. An obese subject gains weight on a diet far below the requirement.

patients individually in a specially designed room which made it possible to observe the subject continuously throughout the twenty-four hours. And we have checked the diets by analyzing samples in our own laboratory. It is certain that the patients received only the energy allowances prescribed by us.

In order to predict the change in weight of an individual who receives food of known caloric value, it is necessary to measure the outflow of energy throughout the period of observation. In the past this requirement has been met only in part. It has been customary to determine the basal metabolic rate and then to make a sophisticated guess regarding the extra calories required for activity and the metabolism of the food. Fortunately we were able to avoid the inaccuracy of such a compilation by modifying a method for measuring heat loss recently described by Benedict and Root.[1] They have shown that the weight of the Insensible Perspiration is parallel to the metabolic rate in the basal state, when certain easily obtained conditions are set up. If the gain or loss of weight for each twenty-four hours is corrected for the weight of the food and drink on the one hand, and for the weight of the urine and feces on the other hand, the resultant is the weight of the Insensible Perspiration for the period.[2] By reference to the appropriate table this value may be directly converted into a statement of the total loss of heat for the twenty-four hours.

With this method at hand we undertook a study of the changes in weight in a normal young man. He remained quietly in bed during the investigation in order to make the requirement for energy as uniform as possible. His diet was restricted to milk and sugar and was always weighed on a good balance by one of us. In addition, the milk was analyzed for nitrogen, fat, solids, and carbohydrate daily.

Under these carefully controlled conditions, it was possible to show that the normal subject would also maintain his body weight or even add to it while he was being underfed. Fig. No. 3 records a gain of 475 grams in five days even though the daily outflow of energy from the subject amounted to 1688 calories whereas he received only 1078 calories. In the face of a daily caloric deficit of 600, he actually added one pound to his weight in five days.

This response of the normal man makes it clear that the ability to maintain the original weight when the diet yields less energy than is used, is not characteristic of any particular type of obesity. Further study showed that it is dependent upon the composition of the diet. Fig. No. 4 represents three consecutive periods in the record of an obese young woman. During the first week she maintains her weight on a diet of 2500 calories. For the next ten days, a diet high in carbohydrate (260 grams daily) that yielded about 1800 calories, was accompanied by a slow steady fall in weight. A sudden shift to a diet of about the same caloric value, but very low in carbohydrate (42 grams daily) resulted first in a rapid loss of weight of short duration, followed by a period nine days long during which no weight was lost. Thus an individual whose

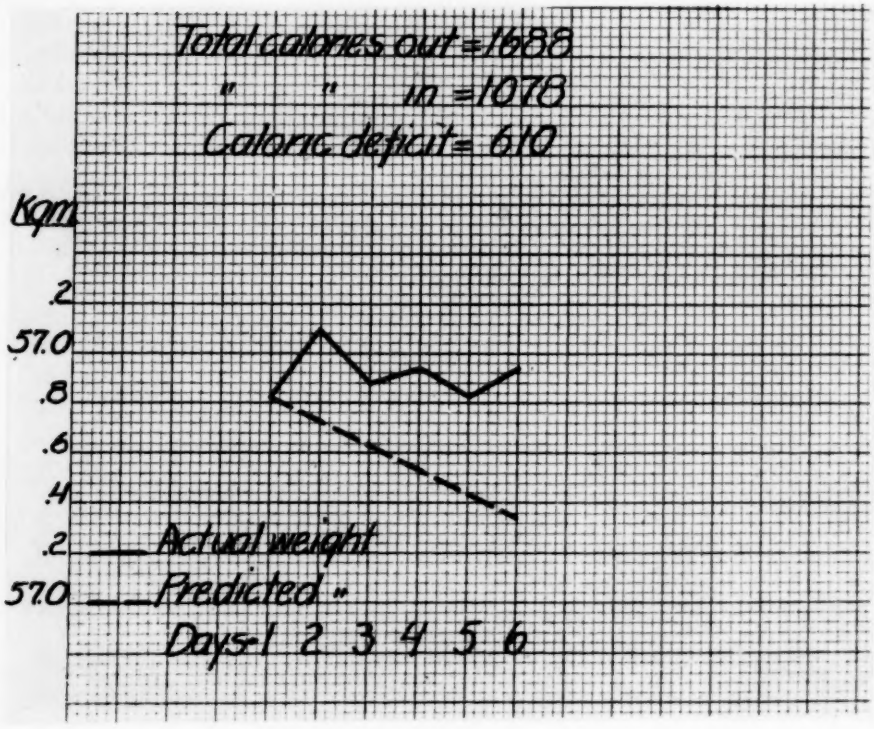


FIG. 3. A normal man gains one pound in five days, on a diet that caused the destruction of one pound of body tissue.

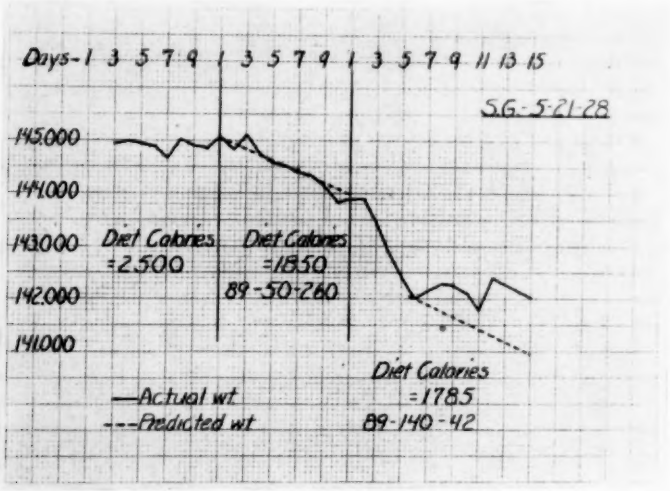


FIG. 4. The composition of the diet determines the shape of the weight curve.

maintenance requirement was 2500 calories, was first made to lose weight progressively and then to maintain her weight, by the successive use of two diets of about equal energy value but widely separated by their content of carbohydrate.

Day to day changes in weight do not reflect the disproportion between inflow and outflow of energy.

How long may an individual maintain his weight in the face of a diet deficient in calories? Does this process continue indefinitely? The literature gives no answer to these questions. Our own observations have shown us that the failure to lose weight is only a matter of days. Thus far the longest period observed by us has been sixteen days. Usually it is shorter. A good example of this phenomenon is seen in Fig. No. 5. This very obese young woman lost essentially no weight for ten days on a diet containing only a little more than half the caloric requirement; in fact she actually made a significant gain in the first two days. Then an abrupt change occurred, consisting of a continuous rapid loss of weight; until, on the thirteenth day, she weighed approximately what had been predicted for her. The prediction was made by converting the caloric deficit for thirteen days into the weight of the adipose tissue that would be oxidized by the subject if her metabolism conducted itself in accord with the physical principles that apply in normal persons.

These departures from the simple

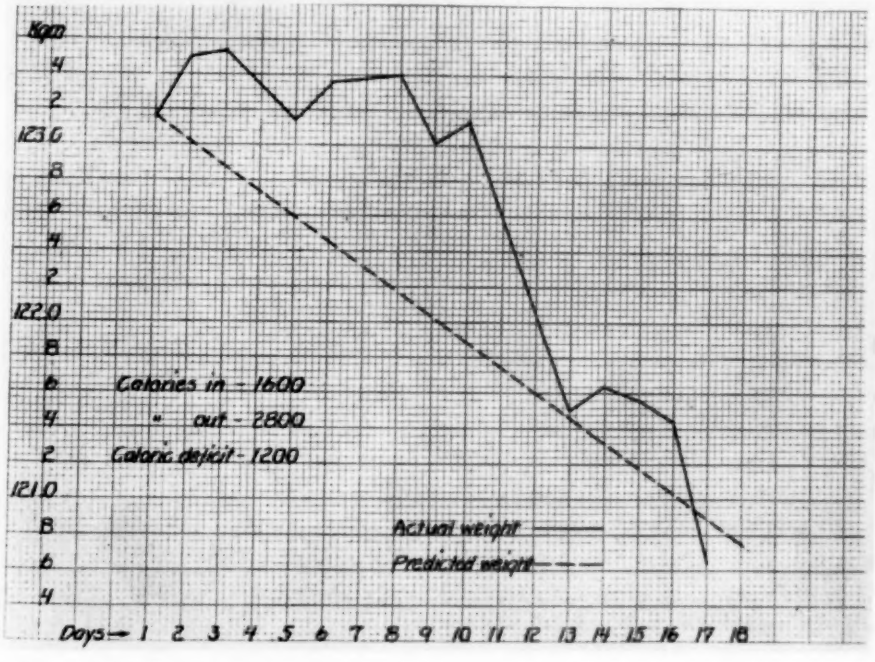


Fig. 5. An obese subject first maintains her weight and then loses weight so rapidly that the total loss corresponds with the prediction.

straight line decline in weight are then firstly of short duration, and secondly always compensated for by a subsequent excessive loss of weight until the total loss corresponds with the expectation. This phenomenon may be produced in the normal subject by suitable adjustment of the diet; accordingly it has no specific significance when it occurs in the obese.

In order to do away with any mystery in connection with the maintenance of weight when the subject is being undernourished, it is in the first place necessary to be able to calculate precisely the weight of the body tissue oxidized to furnish that portion of the energy given out but not contained in the diet. Briefly, this may be done by comparing the total heat production and the total nitrogen output with the energy value and the composition of the diet. This gives the composition and the amount of body tissue destroyed. That is, the predicted loss of weight assuming that no interfering events occur. But the actual changes in weight do not, as a rule, correspond with this simple prediction, whether the subject be obese or normal, undernourished or overnourished.

Since very slight differences in the water content of a mass of protoplasm the size of a human being will amount to pounds in terms of weight, we undertook the difficult task of determining the water exchange[3] in our subjects. With this data at hand it became evident that the organism is very unstable in regard to water; that even when the body is in nutritional balance, it may increase or diminish its percent of water from day to day.

When undernutrition is effected by means of a diet low enough in carbohydrate to cause a large destruction of glycogen, the subject loses weight rapidly for several days while the body is giving up its glycogen, then abruptly enters a second phase during which there is a progressive retention of water by the tissues. After a number of days, this extra water is all given off and at the end of this third phase, the total loss of weight from the inception of the underfeeding corresponds with the calculated weight of the tissue destroyed. The actual results of this type of investigation are exemplified in Table No. 1 and Fig. No. 6 for the normal subject, and in Table No. 2 and Fig. No. 7 for an obese girl with hypophyseal disease.

During the period from which Table No. 1 and Fig. No. 6 was constructed, the normal man dissipated 1818 calories daily. He received 1079 calories in his diet; therefore he obtained 739 calories from the oxidation of his own body tissues. Since he put out 11.8 grams of nitrogen daily but ingested only 10.1 grams, he must have lost from his body the protein which contained the 1.7 grams of nitrogen, not furnished by the diet. This protein weighed 11 grams (1.7×6.25); but as it existed in the living moist state in the body, it weighed 44 grams. The combustion of this 11 grams of protein yielded 44 of the 739 calories derived from the destruction of body tissue. The remaining 695 calories came from the oxidation of 77 grams of fat, which in the form of adipose tissue weighed 85 grams. The weight of the body tissue destroyed each day was accordingly 129 grams.

If 129 be subtracted from the re-

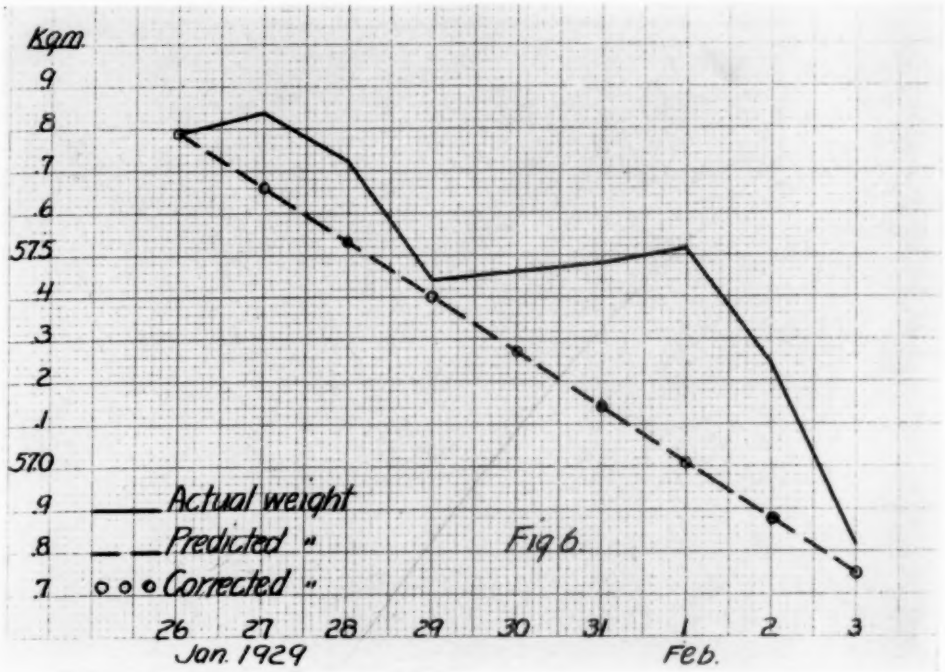


FIG. 6. A normal man gains weight while being undernourished, due to continued retention of water.

corded or actual weight of the subject at the beginning of the period, one obtains a value that indicates what he would have weighed the second day—if that weight reflected merely the loss of body tissue. For example, the weight on the first morning was 57.790 kilograms. The destruction of 129 grams of body tissue in twenty-four hours, would reduce the weight on the second morning to 57.661 kilograms (the Predicted Weight). But the man actually weighed 58.840 kilograms at that time. He had gained 50 grams instead of losing 129 grams. If now the water exchange for this twenty-four hours be examined, it is seen that he added 175 grams of water to his body. The subtraction of this gain in water from the actual weight on the second morning, gives 57.665 kilograms (Corrected Weight), which is what he would have weighed if no water had been retained. This corrected weight is essentially the same as the predicted weight. The evidence accordingly shows that the difference between the actual and the predicted weight was entirely due to retention of water; and supports the statement that the organism did lose tissue in amounts that coincide precisely with the values predicted from the conditions of the experiment.

The application of this same type of study to the obese girl with disease of the hypophysis accounts with equal success for the fact that she lost no weight for sixteen days even though she was destroying 181 grams of body

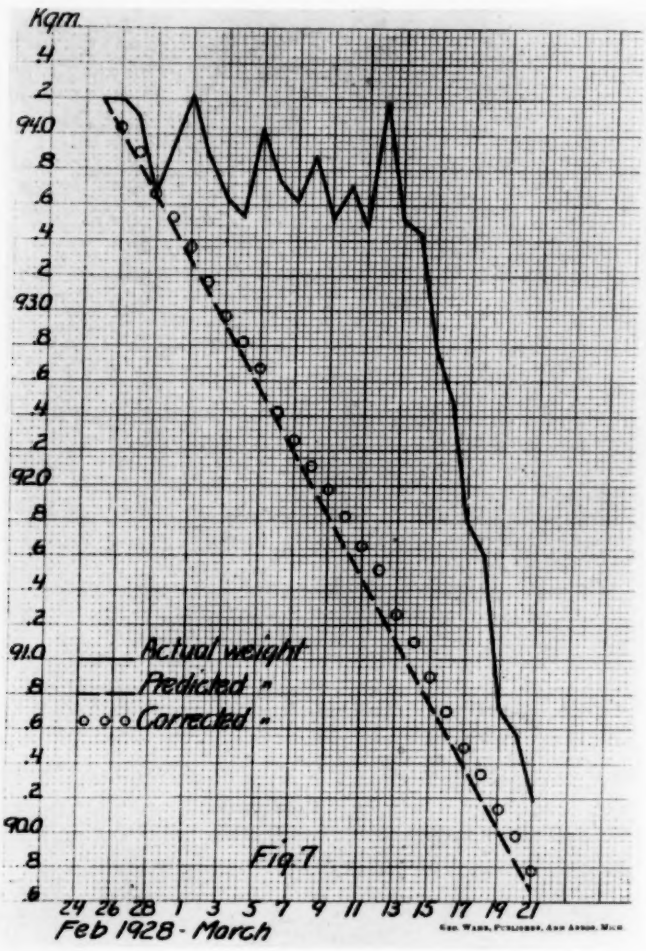


FIG. 7. The same phenomenon in the case of an obese subject with endocrine disease.

tissue daily, and would have lost 2896 grams if the percentile saturation of her body had remained constant. But in fact she retained water in such large amounts that her day to day weights gave no indication that body tissue was being oxidized as predicted.

SUMMARY

It is hoped that this brief review of our studies has made it clear that, when undernutrition is in effect,

(1) An accurate knowledge of the composition of the diet on the one hand, and a satisfactory statement of the total loss of heat and total nitrogen output on the other hand, make it possible to obtain precise information about the kind and amount of body tissue that the subject must destroy to furnish the caloric deficit.

(2) An accurate tabulation of the water exchange shows that body

TABLE I

COMPARISON BETWEEN PREDICTED WEIGHT AND CORRECTED WEIGHT IN THE NORMAL SUBJECT

Date	Actual Weight Kilos	Change in Weight		Water Retention or Loss Grams	Corrected* Weight Kilos	Predicted** Weight Kilos
		Actual Grams	Predicted Grams			
1-26-29	57.790					
1-27-29	57.840	+ 50	—129	+175	57.665	57.661
1-28-29	57.725	—115	—129	+ 33	57.517	57.532
1-29-29	57.440	—285	—129	—147	57.379	57.403
1-30-29	57.465	+ 25	—129	+139	57.265	57.274
1-31-29	57.480	+ 15	—129	+129	57.151	57.145
2- 1-29	57.515	+ 35	—129	+175	57.011	57.016
2- 2-29	57.245	—270	—129	—153	56.894	56.887
2- 3-29	56.815	—430	—129	—293	56.757	56.758

*These are the actual weights, plus or minus water lost or retained by the organism during the preceding twenty-four hours.

**This is what the subject would have weighed on each day, if his weight had been affected solely by the loss of body tissue destroyed during the preceding twenty-four hours.

TABLE II

COMPARISON BETWEEN PREDICTED WEIGHT AND CORRECTED WEIGHT IN AN OBESE SUBJECT

Date	Actual Weight Kilos	Change in Weight Actual Grams	Change in Weight Predicted Grams	Water Retention or Loss Grams	Corrected* Weight Kilos	Predicted** Weight Kilos
2-25-28	94.200					
2-26-28	94.200	0	—181	+157	94.043	94.019
2-27-28	94.115	— 85	—181	+ 66	93.892	93.838
2-28-28	93.635	—480	—181	—249	93.661	93.657
2-29-28	93.935	+300	—181	+448	93.513	93.476
3- 1-28	94.215	+280	—181	+428	93.365	93.295
3- 2-28	93.865	—350	—181	—144	93.159	93.114
3- 3-28	93.635	—230	—181	— 39	92.968	92.933
3- 4-28	93.525	—110	—181	+ 42	92.816	92.752
3- 5-28	94.025	+500	—181	+650	92.666	92.571
3- 6-28	93.735	—290	—181	— 48	92.424	92.390
3- 7-28	93.625	—110	—181	+ 44	92.270	92.209
3- 8-28	93.885	+260	—181	+396	92.134	92.028
3- 9-28	93.525	—360	—181	—210	91.984	91.847
3-10-28	93.695	+170	—181	+338	91.816	91.666
3-11-28	93.470	—225	—181	— 79	91.670	91.485
3-12-28	94.190	+720	—181	+872	91.518	91.304
3-13-28	93.525	—665	—181	—411	91.264	91.123
3-14-28	93.435	— 90	—181	+ 71	91.103	90.942
3-15-28	92.795	—640	—181	—434	90.897	90.761
3-16-28	92.495	—300	—181	—107	90.704	90.580
3-17-28	91.795	—700	—181	—486	90.490	90.399
3-18-28	91.600	—195	—181	— 48	90.343	90.218
3-19-28	90.725	—875	—181	—673	90.141	90.037
3-20-28	90.575	—150	—181	+ 13	89.978	89.856
3-21-28	90.195	—380	—181	—191	89.789	89.675

*These are the actual weights, plus or minus water lost or retained by the organism during the preceding twenty-four hours.

**This is what the subject would have weighed on each day, if his weight had been affected solely by the loss of body tissue destroyed during the preceding twenty-four hours.

weight is the resultant of two factors, namely (1) gain or loss of tissue and (2) a gain or loss of water. The loss of one and a gain in the other may neutralize each other; or a large retention of water may cause a gain in weight even though body tissue has been consumed; and may lead an observer, who fails to take water exchange into account, to draw erroneous conclusions.

(3) The response of various types of obese people does not differ from that of normal people. All of them oxidize body tissues in accord with the prediction from the caloric deficit.

Conclusions

Obesity is always caused by an overabundant inflow of energy. The excess is deposited as adipose tissue. This disproportion arises from a variety of conditions that may be thought of under two general headings. The first group includes the various human weaknesses such as over-indulgence and ignorance. The second group is composed of conditions that cause a decrease in the requirement for energy; such as lessened activity or lowering of the basal metabolic rate for any reason. If the long established food habits do not respond to this lessened demand, obesity is inevitable.

References

[1]Benedict, F. G. and Root, H. F.: Insensible Perspiration; Arch. Int. Med., 1926, Vol. 38, p. 1.

[2]Johnston, M. W., Newburgh, L. H., The Determination of Total Heat Elimination; J. Clin. Invest., Feb., 1930. Invest. Feb., 1930.

[3]Newburgh, L. H., Johnston, M. W., and Falcon-Lesses, M.: The Determination of Water Exchange; J. Clin. Invest. 1930, Vol. —, p. —.

[4]Newburgh, L. H., Johnston, M. W., and Falcon-Lesses, M.: The Nature of Obesity; J. Clin. Invest. 1930.

The Use of Sodium Malate Combinations as a Dietary Substitute for Sodium Chloride.

By John C. Krantz, Jr., Ph.D., *Baltimore, Md.*

INTRODUCTION: The prevalence of the prescribing of the diet of salt restriction for patients suffering with chronic interstitial nephritis, edema or hypertension is emphasized by Allen[1] who estimates this number to be more than two million in the United States. Although the most enthusiastic advocates of the diet of salt restriction claim beneficial results in cases of nephritis, edema and hypertension, little evidence is available in the literature indicating work upon the production of sodium chloride substitutes to increase the palatability of the salt restricted diet. In 1912 Javal[2] suggested the use of sodium bromide or iodide to improve the taste of unsalted bread. In many respects these compounds are as objectionable in the foregoing conditions as sodium chloride itself. Tueteur[2a] described a double calcium salt of polyaminic acid which he claims to have a salty taste.

With the purpose of discovering some compound (or mixture of compounds) that would play the rôle in the diet of salt restriction, that saccharin plays in the diet of sugar restriction, this investigation was begun.

Selection of Compounds: The outstanding characteristic of a substitute for sodium chloride as a condiment is the production of a characteristic "saltiness" when employed upon food. Unless the substance is characterized by the taste of sodium chloride, no matter how many other desirable characteristics it may possess, it is worthless as a salt substitute.

Aromatic organic compounds were not considered on account of their toxic nature when used in quantities of four to five grams a day. The physical natures (liquid state, disagreeable odor, etc.) of thousands of aliphatic compounds eliminated these from consideration. The toxic nature of the ions of the heavy metals, the similarity to sodium chloride of many of the compounds of the alkali metals precluded these as possibilities. All inorganic acids and bases were considered unsuited for this purpose. The fact that the agreeable salinity of sodium chloride is dependent upon the chlorine ion, and not the sodium ion, led to the careful consideration of the sodium salts of the acids obtained by mild oxidation of certain carbohydrates, for an acid radical which resembled the chlorine ion in taste. Further, an acid of high molecular weight was considered desirable for this would reduce the percentage of sodium

in the molecule. Sodium gluconate, sodium mucate and sodium saccharate were found to be practically useless for this purpose—the tastes of these compounds did not resemble that of sodium chloride. In addition to this, certain investigators[3] have shown the nephropathicity of these acids.

The next series of compounds investigated were the fruit acids, most of which are hydroxy acids of the methane series of hydrocarbons. Tartaric and lactic acids salts were not suitable on account of the fact that the former had been shown by Underhill et al.[4] to produce kidney damage and the sodium salt of the latter was not strongly saline. The sodium salt of citric acid was somewhat saline, yet its taste was not nearly so desirable as that of sodium chloride. Sodium citrate presented itself as a possibility in view of the work of Salant and Wise[5] who showed that sodium citrate, when given in reasonably large doses, was not toxic to rabbits. These investigators found only negligible quantities of the sodium citrate in the blood and urine after the ingestion of large quantities of the salt.

In the further study of the fruit acids, malic acid (which is present to the extent of 0.6% in apples) was studied. The sodium salt of this acid was found to have a taste almost identical with that of sodium chloride. After overcoming many of the difficulties of drying the syrupy mass obtained in the evaporation of solutions of sodium malate, this was mixed with various other materials in varying proportions in order to enhance its salt-like taste. These mixtures contained large percentages of sodium malate, with small quantities of ammonium and sodium citrates to which about one-half of one per cent of manganese bromide was added. This small quantity of manganese bromide was found desirable to enhance the agreeable salty taste of the mixture. Furthermore, the fact that the halides of manganese are inappreciably ionized made manganese bromide especially suited for the purpose intended. Just as the chemist names the undiscovered elements in the periodic system eka idoine, eka caesium, etc., for convenience, in the laboratory the saline mixture was designated as eka salt.

Organoleptic Tests: Various sodium malate mixtures were employed on food by healthy individuals in place of sodium chloride as a condiment—the similarity in taste between eka salt and sodium chloride was agreed upon by those using it. Eka salt was placed in the salt shakers on the table in three different homes without the knowledge of the members of the family—these folks used eka salt in place of sodium chloride without becoming aware of the substitution.

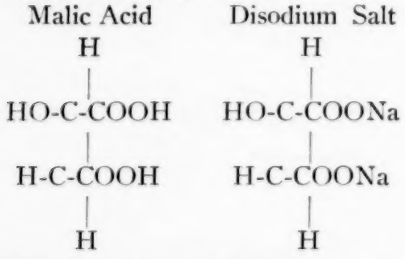
In the laboratory triturations were made with eka salt and sodium chloride separately in barium sulphate as a dispersion medium in order to determine the vanishing points of salinity by the organoleptic tests. Eka salt by this method possessed 7/8 the salinity of sodium chloride.

This mixture consisted of 85.5 per cent sodium malate, 9 per cent citrate, 5 per cent ammonium citrate and 0.5% manganese bromide. There is a possibility that in the preparation of the salt that double decomposition ensues

in part between the ammonium citrate and a portion of the sodium malate.

Physical Properties of Eka Salt: Eka salt occurs as a white granular powder, which is readily soluble in its own weight of water. A ten per cent solution of the salt has a pH between 7 and 8, measured by means of the hydrogen-electrode. The specific gravity of eka salt is 1.8, that of sodium chloride is 2.16, i.e., eka salt is 14 per cent less dense than sodium chloride. The osmotic pressure of sodium chloride in 0.1N. solution, measured by the depression of the freezing point method, is 4.28 atmospheres, that of eka salt in the same concentration (expressed in grams) is 2.059 atmospheres, i.e., the osmotic pressure of sodium chloride is 108 per cent greater.

The Chemistry and Metabolism of Eka Salt: Malic acid was isolated first by Scheele in 1785 from green apples. The acid chemically is monohydroxy-dicarboxy-ethane or



The levorotatory compound occurs in nature, whereas the synthetic variety used in the preparation of eka salt is the racemic form. This is synthesized by the catalytic oxidation of benzene by air through maleic acid as described by Downs.[6] Ohta,[7] Wise,[8] Underhill and Pack[9] and Rose[10] have studied the metabolism of salts of malic acid on various experimental animals and have demonstrated the fact that malic acid in reasonable quantities (10 to 12 Gm. to rabbits) is completely metabolized and devoid of toxic action. The amount of malic acid ingested by one using 4 gm. of eka salt is equivalent to the amount of malic acid contained in two average sized apples. The same quantity of eka salt introduces into the system about as much citric acid as one would obtain from about one-tenth of a lemon.

The presence of such small quantities of the salts of citric acid and the fact that manganese (0.5% in the form of bromide) has been shown by Bargero[11] to be eliminated in the feces as sulphide, reduces the problem essentially to the study of the metabolism of sodium malate.

Influence of Eka Salt upon Chloride Elimination: Dogs were fed a diet of milk and biscuit of definite chloride content. The urine was collected daily over five days and the chloride content determined.

TABLE I.

Dog No. 1. Average NaCl output in 24 hrs.
2.44 Gm.

Dog No. 2. Average NaCl output in 24 hrs.
2.51 Gm.

Upon the same diet the dogs were fed 5 Gm. eka salt daily and over a period of eight days the chloride elimination in the 24-hour specimen of urine was determined.

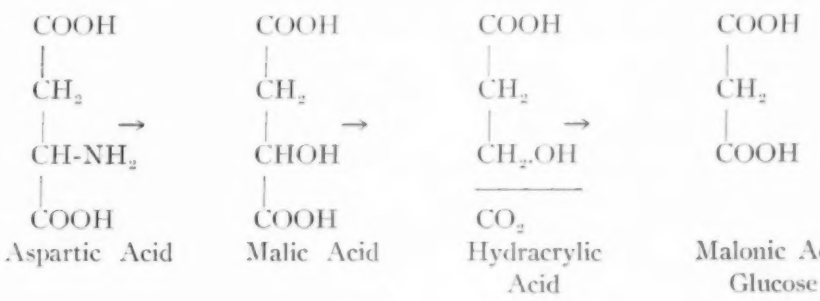
Dog No. 1. Average NaCl output in 24 hrs. with eka salt
2.28 Gm.

Dog No. 2. Average NaCl output in 24 hrs. with eka salt
3.07 Gm.

When the eka salt was replaced by 5 gm. of sodium chloride the chloride content of the urine was increased by 76 to 94% of the amount of chloride ingested which appeared in the urine in addition to that chloride from the standard diet.

This is indicative of the fact that eka salt when ingested does not cause an increased chloride elimination by the kidney.

The Fate of Malic Acid: Malic acid is a substance which is not foreign to the human metabolic process when protein is ingested, for it is formed in the metabolism of aspartic acid which is present in most protein bodies. Ringer et al.[12] have shown the following metabolic changes occur:



To confirm this work these investigators demonstrated that malic acid would give rise to extra glucose in phlorhizinized animals.

To confirm this work in man, an individual was fed 4 gm. of Eka salt daily for five days and the usual twenty-four hour urine specimens collected and examined qualitatively for malic acid. The author was unable to find malic acid in the urine indicating its catabolism as previously suggested.

The urine was examined for malic acid as follows: Evaporate 10 c.c. of acidified urine to dryness, extract the residue twice with 15 c.c. of boiling ether. Evaporate the etherial extractions to dryness and add 1 c.c. of a freshly prepared solution of beta naphthol 0.1 Gm. in 5 c.c. of concentrated sulphuric acid.[13] Warm over a water-bath for 30 to 60 seconds and then add 10 c.c. of water. In the presence of malic acid (which is extracted by the ether) a yellow color develops which fades upon standing. With urine the test was found sensitive to 1 mgm. of malic acid in 1 c.c.

This experiment would seem to indicate that in the ingestion of 4 gm. of eka salt, the maximum quantity generally employed as a condiment, the malic acid present would be completely metabolized.

The Fate of Sodium: The ideal substitute for sodium chloride in the diets of salt restriction would be one that contained no metallic ion at all. The present author was unable to find such a substance, but in the composition of sodium malate this objection is reduced to a minimum. In the ingestion of sodium malate (after the metabolism of the malate radical) the sodium atom would at first add to the alkali reserve of the blood and be com-

pensated by the acids arising during the normal metabolism of proteins. It is therefore likely that the excretion of the alkali takes place as follows:

$$NaH_2PO_4 + Na\ A \rightarrow \underset{\text{To urine when less acid}}{Na_2HPO_4} + \underset{\text{acid metabolized}}{H\ A\ *}$$

This reduction of urine acidity under similar conditions was studied by Underhill and Wakeman.[14]

To substantiate the validity of this view of the metabolism of eka salt a normal individual was placed on a diet of reasonable uniformity and twenty-four-hour specimens of the urine collected and the nitrogen, phosphorus and hydrogen-ion determinations were made. The nitrogen and phosphorus were determined by the well-recognized methods and the hydrogen-ion determination made by the electrometric method using a Wilson electrode.[15] Table II gives the results of these determinations.

From Table II it was determined that the average total nitrogen eliminated in twenty-four hours without eka salt was 8.55 gm. Over the same number of days with eka salt the average nitrogen elimination in 24 hours was 8.39 gm. The average phosphorus elimination estimated as P_2O_5 without eka salt was 1.88 gm., with eka salt the average elimination was 1.90 gm. P_2O_5. These results indiçate that the ingestion of eka salt in this amount does not influence the nitrogen or phosphorus elimination.

A very significant change in the pH of the urine can be readily observed from the table. The ability to replicate this change on the same individual is of special interest. The arithmetic average of the pH determinations of the urine without eka salt is pH 5.97—with eka salt the average pH is 6.96. Determining the Probable Error in this series of determinations according to the formula

$$P.\ E. = 0.8453 \times \frac{\Sigma\ D}{N}$$

where D is the average deviation and N the number of observations, the Probable Error in the case of the observations made without eka salt is 0.26 pH or 4.4% and with the observations made with eka salt the Probable Error is 0.24 pH or 3.51%.

The influence of eka salt upon the acid-base equilibrium of the urine is readily seen in graph No. 1.

The decreased acidity of the urine seems to be desirable in nephritis; Fischer[16] claims the presence of acid in the urine favors the solution of kidney colloids and may produce albuminuria. This investigator contends also that base-yielding foods are desirable in nephritis. Eka salt serves as a base-yielding condiment.

Sodium-Ion Elimination: In restricting salt from the diet of the nephritic the physician is interested usually in reducing the number of particles (ions and undissociated mole-

*Where HA represents malic acid.

TABLE II.
EKA SALT METABOLISM

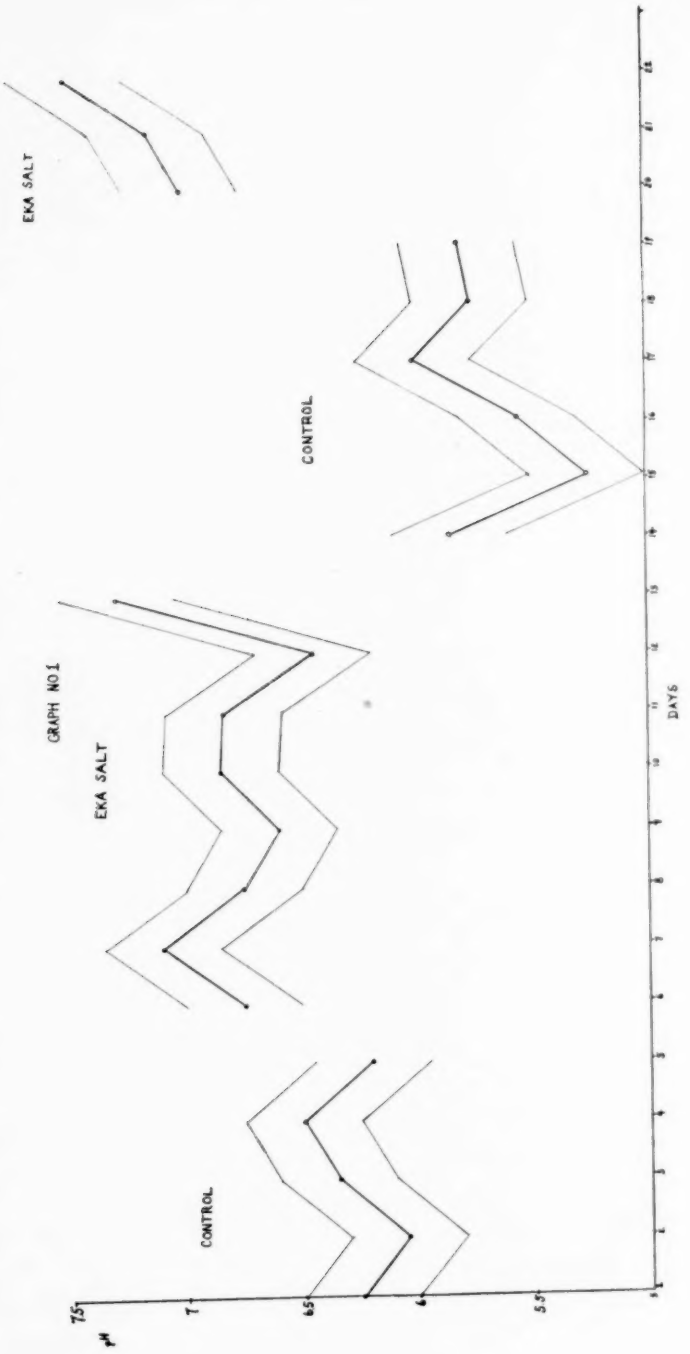
Date		Volume in c.c.	pH	gm. of P_2O_5 in 24 hrs.	$\%P_2O_5$	gm. of N_2 in 24 hrs.	$\%N_2$
No Eka	2/14/29	650	6.26	1.76	0.271	6.92	1.06
No Eka	2/15/29	730	6.08	1.60	0.219	8.03	1.10
No Eka	2/17/29	820	6.36	1.83	0.223	7.98	0.97
No Eka	2/18/29	925	6.50	1.86	0.202	6.99	0.76
No Eka	2/19/29	710	6.21	1.94	0.273	8.37	1.15
Eka	2/21/29	810	6.75	1.81	0.224	6.23	0.77
Eka	2/22/29	950	7.27	1.50	0.158	7.11	0.75
Eka	T/23/29	1,030	6.75	2.26	0.220	8.08	0.78
Eka	2/24/29	1,290	6.61	2.60	0.202	11.01	0.85
Eka	2/25/29	810	6.85	2.07	0.256	8.39	1.04
Eka	2/26/29	780	6.84	1.63	0.210	8.03	1.03
Eka	2/27/29	900	6.47	2.20	0.234	11.03	1.23
Eka	2/28/29	875	7.30	1.33	0.164	8.88	1.02
No Eka	3/ 1/29	785	5.85	2.15	0.271	9.73	1.24
No Eka	3/ 2/29	720	5.24	2.11	0.294	10.13	1.41
No Eka	3/ 3/29	700	5.58	1.84	0.264	9.41	1.34
No Eka	3/ 4/29	750	6.03	1.78	0.238	8.35	1.11
No Eka	3/ 5/29	535	5.75	1.85	0.346	8.28	1.55
No Eka	3/ 6/29	775	5.81	1.93	0.250	9.93	1.28
Eka	3/ 7/29	1,140	7.08	2.07	0.182	7.82	0.69
Eka	3/ 8/29	960	7.18	2.07	0.216	6.79	0.71
Eka	3/ 9/29	615	7.52	1.32	0.218	9.01	0.93

cules) necessary for the impaired organ to eliminate. With eka salt there is no increased chlorine-ion elimination and the elimination of the sodium-ion ingested based upon the above experiments reduces itself to a definite mathematical basis.

Eka salt contains 24.4 per cent of sodium (Na). The ingestion of 4 gm. therefore results in 4 X 0.244 = 0.976 gm. No. To supply this amount of sodium from NaCl would require

NaCl=58.4 and Na=23

$$\frac{58.4}{23} = 2.5 \times 0.976 = 2.44 \text{ gm. NoCl}$$


GRAPH NO 1
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In 0.1 M. solution NaCl is 84% ionized. The molarity of a solution of NaCl containing 2.44 gm. NaCl is

$$\frac{2.44}{58.4} = 0.0417 \text{ molar.}$$

In this concentration assuming ionization 90% complete we have

$0.0417 \times 0.90 = 0.03752$ conc. of Na^+ hence the total $[Na^+]$ $[Cl^1]$ and $[NaCl] = 0.0797$ mole particles for kidney elimination when 2.44 gm. of NaC is ingested. Considering now eka salt, we have

$$NaH_2PO_4 + Na \text{ forming } Na_2HPO_4$$
$$120 \qquad 23 \qquad 142$$

From one gram Na approximately 6 gm. of Na_2HPO_4 result.

Expressing in molar concentration, we have

$$\frac{6}{142} = 0.042 \text{ molar}$$

In this concentration disodium phosphate is about 75% ionized. Therefore $0.042 \times 0.75 = 0.0315$ conc. Na^+ hence the total $[Na^+]$ $[HPO_4'']$ and $[Na_2HPO_4] = 0.1045$ mole particles for the kidneys to eliminate with 4 gm. eka salt containing 0.976 gm. Na or approximately 1 gm. Na.

But there exists prior to the ingestion of the Na in the eka salt the NaH_2PO_4 which would require 0.073 mole for the kidney elimination.

Hence the ingestion of eka salt is responsible for the difference between these values or $0.1045 - 0.073 = 0.0315$ mole particles added by 4 gm. eka salt. Comparing this with NaCl calculated above, when only 2.44 gm. is ingested the Na^+ and Cl and NaCl molecules were 0.0797 molar.

$$\text{Therefore } \frac{0.0797}{0.0315} = 2.53$$

that is, there are 2.53 per cent more particles eliminated from the Na in the form of NaCl than the same amount of Na in the form of eka salt.

Clinical Use: During the past year in the hands of several clinicians of this city and its vicinity eka salt has been used as a dietary substitute for table salt in various conditions where a diet of salt restriction was prescribed. In all cases (numbering about 150) the patient found eka salt an adequate dietary substitute for table salt. In no instance did the attending physician report any untoward effects. The results of the clinical findings during the use of this sodium chloride substitute will be reported in a subsequent communication.

Conclusions

1. The metabolism of certain sodium malate combinations has been studied.
2. A dietary substitute for sodium chloride in the diets of salt restriction has been described.
3. Certain advantages of this substance, eka salt which is essentially sodium malate, over sodium chloride in salt-restricted diets have shown experimentally.

Throughout this investigation the author has been indebted to Mr. C. Jelleff Carr for his technical assistance.

BIBLIOGRAPHY

[1]Allen, F. M.: New York State Med. J. (1925), *25*, 728.

[2]Javal, M. A.: Zentr. Bioch. Hioph., (1912), *14*, 526.

[2a]Tuteur-Klin. Wochenschrift No. 37 (1918) 2467.

[3]Rose, W. C. et al.: J. Pharm. Exp. Therap., (1925), *25*, 59.

[4]Underhill et al.: J. Exper. Med., (1913), *18*, 322 and 347.

Rose, W. C.: J. Pharm. Exp. Therap., (1925), *24*, 123.

[5]Salant, W. and Wise, L. S.: Journ. Biol. Chem., (1916), *28*, 27.

[6]Downs, C. R.: U. S. Patent 1,374,720, Chem. Abs., (1921), *15*, 2641.

[7]Ohta, K.: Biochem. Z., (1912), *44*, 482.

[8]Wise, L. E.: Journ. Biol. Chem., (1916), *28*, 185.

[9]Underhill and Pack: J. Pharm. and Exp. Therap., (1925), *25*, 467.

[10]Rose, E. C.: J. Pharm. and Exp. Therap., (1925), *24*, 123.

[11]Bargero: Biol. Chem. Centr., (1906), *5*, 504.

[12]Ringer, Frankel and Jones: J. Biol. Chem., (1913), *14*, 539.

[13]Mulliken: Identification of Pure Organic Compounds, p. 83, Wiley & Sons.

[14]Underhill and Wakeman: J. Biol. Chem., (1922), *54*, 701.

[15]Wilson: J. Ind. and Eng. Chem., (1925), *17*, 74.

[46]Fischer, M. H. J.: Am. Med. Assn., (1914), *60*, 1682.

Typhoid Fever Complicated By a Perforated Gangrenous Appendix*

Report of a Case with Recovery

By Mitchell Bernstein, M.D., *Philadelphia, Pa.*

APPENDICITIS complicating typhoid fever is not of frequent occurrence, but failure to recognize this important complication may prove of serious consequence. Statistics reveal the total typhoid fever death rate for seventy-four cities of the United States during 1928 at 1.89 per 100,000 population.[1] Some of these deaths were doubtless due to complications such as perforation and hemorrhage. In addition, appendicitis complicating typhoid fever, unless recognized and properly treated, may end fatally, because of suppuration, perforation, or both.

Previous attacks of appendicitis predispose to an acute flare-up at any time during the course of typhoid fever. The symptoms may be so slight as to escape attention. However, the occurrence of acute pain in the right lower abdomen together with tenderness and spasm of the right lower abdominal muscles, with a temporary fall of the temperature, with or without diarrhea, during the course of typhoid fever, should suggest the possibility of a complicating appendicitis. An increase in the total number of leukocytes together with a rise in the polymorphonuclear count is of the greatest importance in diagnosis. Shock, which is usually present in perforation, is generally absent. While the appendiceal symptoms occasionally subside, the inflammation may go on to suppuration and lead to final rupture.

The following case report is illustrative of the latter complication. This case would probably have ended fatally and would have been classified as a death due to typhoid fever, were it not for the fact that proper diagnosis and surgical intervention avoided fatality.

Case report:—On February 6th, 1929, D. H., female, 14 years of age, was admitted to the medical service of Dr. Bernard Kohn, at the Jewish Hospital, complaining of severe headaches and fever. The patient stated that these symptoms had been present for eight days prior to her admission. She had previously been a patient in the hospital, having been there from November 25th, 1928, to January 19th, 1929, with influenza. During this time she was in close association with another patient who had typhoid fever.

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[1] J. A. M. A., 92: No. 20, pp. 1677, 1929.

On admission the patient's temperature was 103.6°F., the pulse rate was 110, and the respiratory rate was 22 per minute. Her face was flushed. She had an anxious expression. There was no jaundice. The mouth was dry, the tongue was heavily coated, and the breath was foul. Examination of the neck revealed no abnormality. Examination of the chest revealed a left-sided pleural effusion which extended up to the eighth rib posteriorly. (This pleural effusion was present at the time of her previous discharge from the hospital on January 19th, 1929, repeated examinations of the pleural fluid having failed to reveal any evidence of a tuberculous nature.) The breath sounds at the apex of the left lung were slightly exaggerated, the lungs otherwise being apparently normal. The heart was slightly displaced to the right but was normal in size. On auscultation a faint systolic murmur, with transmission to the left axilla, was heard in the fifth left interspace. The blood pressure was 100 mm. systolic and 60 mm. diastolic. Examination of the abdomen revealed a few scattered rose spots. The abdomen was slightly distended, but there was no tenderness or rigidity. The spleen was not palpable although it was slightly enlarged on percussion. The extremities were negative.

Examination of the urine was negative. A leukocyte count showed 8200 cells with 75% polymorphonuclear, 23% small mononuclear and 2% large mononuclear cells.

On February 8th, two days following admission, the Widal reaction was positive for typhoid fever.

On February 11th, five days following admission, the patient complained of pain in the lower right abdomen associated with vomiting. The abdomen at this time was slightly distended. The leukocyte count showed 8000 cells with 87% polymorphonuclear and 13% small mononuclear cells. The pain and vomiting continued the following day and there was also some diarrhea. There was some rigidity of the lower right abdominal muscles. The next day the pain in the lower right abdomen became unbearable, and there was exquisite tenderness and muscle spasm over this area. Rectal examination revealed tenderness on the right side. The leukocyte count was 11,000 with 87% polymorphonuclear and 13% small mononuclear) and later the same day the blood count showed 14,400 leukocytes and 89% polymorphonuclear with 11% small mononuclear cells. The temperature which had varied from 102° to 104.6°F. dropped gradually to 100°F. at this time. The pulse rate which had averaged 110 per minute dropped to 90 per minute for a short interval and then continued at the average rate of 120 per minute. A diagnosis of perforated gangrenous appendix complicating typhoid fever was made and confirmed by Dr. William H. Teller, who advised conservative treatment temporarily, consisting of Murphy proctoclysis and heat to the lower right abdomen.

During the following nine days the patient's temperature was of septic type, ranging from 99° to 104.6°F., and the pulse averaged 120 per minute. The tenderness and muscle spasm remained unchanged in the lower right

abdomen and the percussion note over this area was markedly impaired. Rectal examination revealed a bulging mass in the right side.

On February 22nd, 1929, Dr. William H. Teller operated upon the patient and found a perforated gangrenous appendix with secondary involvement of the right fallopian tube. Drainage was necessary. Culture from the pus obtained at operation was negative for typhoid bacilli but positive for colon bacilli. The Widal reaction on February 23rd-24th and later on April 10th remained positive for typhoid fever. The course subsequent to operation was uneventful. The temperature became normal on March 2nd, 1929, eight days following operation, this being the thirty-second day of the illness.

The blood chemistry was constantly normal. Repeated examinations of the urine showed a varying specific gravity from 1.004 to 1.028, no sugar, an occasional trace of albumin and at times a few hyaline casts.

The patient was discharged from the hospital on April 11, 1929, in good condition except for a slight opening of the operative wound which closed completely on July 3rd, 1929, as reported by her physician, Dr. Harold Lipshutz.

Conclusion:—The case herein reported emphasizes the importance of the recognition of acute appendicitis complicating typhoid fever, and the necessity for proper surgical intervention.

The Acid-Base Composition of Gastric Juice During the Secretory Cycle*

By Theodore L. Bliss, M.D., *Fellow in Medicine, The Mayo Foundation, Rochester, Minnesota*

MANY determinations have been made of the acids and the total chlorides in the gastric secretion, but only a few of the other inorganic constituents. All observers have found that there is an increase in the concentration of the total acid and free hydrochloric acid in the normal gastric secretion following stimulation. However, observers have found differences in the response of the chlorides to stimulation. Berglund, Wahlquist and Sherwood found that the concentration of chlorides was essentially equal to that of the hydrochloric acid titrated in the secretion from a human subject having an acidity range within normal limits, after stimulation by histamine. They concluded that such a gastric juice contained little, if any, chloride in combination other than with hydrochloric acid. Bulger and Allen, and Bulger, Stroud and Heideman found that the concentration of chloride did not vary markedly in mixed gastric secretion after stimulation by a water meal, and concluded that chlorides were secreted into the stomach at a rate which was practically constant. Gamble and McIver obtained similar results in the secretion from pouches of the fundus of cats, using various types of food for stimulation, and drew the same conclusions. Polland, Roberts and Bloomfield, on the other hand, found that the concentration of chloride promptly increased in mixed gastric secretion of human beings after stimulation with histamine to a maximum which occurred at the same time as the maximal concentration of acid. Later in the cycle, the concentration of the acid tended to fall more quickly, whereas that of the chloride fell slowly. They also found that the concentration of chloride exceeded the concentration of the hydrochloric acid titrated, and believed that some of the chloride was combined in other forms. This excess of chloride was largely accounted for by base. They calculated the total chloride output in the various phases of the gastric cycle on the basis of the volume of the secretion recovered in each phase. This showed an absolute increase in the output of chloride which did not correspond to the respective increase in concentration in the majority of cases. They believed this indicated that at a

*This work was done under the supervision of Dr. Leonard G. Rowntree, Division of Medicine, The Mayo Clinic and The Mayo Foundation. Submitted for publication August 16, 1929.

given concentration the actual amount of chloride secreted may vary considerably. Close found that the concentration of chloride in a mixed secretion varied in the same manner as the concentration of the free hydrochloric acid after stimulation with histamine, the former always exceeding the latter.

If this excess of chloride over the concentration of free hydrochloric acid under these conditions is evidence of the presence of inorganic chloride in the gastric juice, it may be used as an approximate index of the amount of inorganic base present. Only a few observers have determined the total base in gastric secretion directly. Rosemann determined the sodium, potassium, calcium and magnesium in pooled specimens of a mixed secretion from the pylorus and fundus of a dog after stimulation with food through an operative esophageal fistula, and from them calculated the total base. More recently, Gamble and McIver determined the total base in the secretion from isolated pouches of the pylorus and fundus of dogs; the secretion was collected at various intervals following stimulation with different types of food. Bulger, Stroud and Heideman used a water meal to stimulate gastric secretion in human subjects, and determined the total base in it after correction for the volume of the water meal. Polland, Roberts and Bloomfield determined the base in mixed gastric secretion of human subjects collected fractionally after stimulation with histamine. They also calculated the output of base in each period of the gastric cycle on the basis of the volume of secretion which was recovered. Close determined the total base in such secretion, and in the secretion from the Pavlov pouch of a dog, both of which had been collected fractionally after stimulation with histamine. These investigators obtained essentially the same results. They all found that the concentration of base in the fasting content was greatest in cases of achlorhydria and lowest in the cases of hyperchlorhydria. After stimulation the concentration of base decreased as the concentration of free hydrochloric acid increased, the relative degrees of variation in each being roughly proportional. Close further found that the concentration of base was increased after stimulation, in four cases of achlorhydria, but did not proffer an explanation. Polland, Roberts and Bloomfield found that the actual amount of base, as compared to the concentration values, was increased after stimulation so that it varied in the same manner as the free hydrochloric acid. They believed this indicated that stimulation resulted in the activity of all types of gastric secretory cells. So far as I know, Rosemann alone has determined the constituents of gastric base. Gamble and McIver determined the potassium and calcium and calculated the sodium by subtracting the sum of the potassium and calcium from the total base. They disregarded the magnesium, since Rosemann had found it present in such small amounts.

This report deals with determinations of the acid titrated, the chloride, the fixed base and its various constituent cations, sodium, potassium, calcium and magnesium, in the fasting gastric content, and their changes dur-

ing the successive periods of the gastric secretory cycle following gastric stimulation with histamine.

Method of Experiment

The gastric secretion in these experiments was collected from two healthy laboratory workers, from one patient, and from a dog with a Pavlov pouch. The human subjects were fasted for fourteen hours previous to the intubation, and were urged to minimize the amount of saliva swallowed for several hours prior to, and during, the experiment. The usual Rehfus tube was passed and the stomach emptied as completely as possible by gentle aspiration. This material has been taken to represent the fasting content. Then 0.1 mg. of histamine was given hypodermically and the resultant secretion aspirated as completely as possible at the end of each fifteen-minute interval for one hour, at which time the gastric cycle was deemed to be essentially completed. In two instances, continuous aspiration was attempted by means of siphonage, in an effort to recover the entire secretion in each phase of the cycle. The presence of grossly visible bile was taken as an index of duodenal regurgitation and when it appeared the experiment was terminated forthwith. Bile was not grossly visible in any of the experiments presented here. The amount of histamine used did not in any instance cause an untoward reaction. Similar experiments were carried out on a dog with a Pavlov pouch. This afforded a secretion from the fundus rather than a mixed secretion, but one which was not contaminated by saliva or regurgitated duodenal contents. The dog was fasted for fourteen hours, then the pouch was drained for one hour and the material was taken to represent the fasting content. Since it had been shown that larger doses of histamine prolonged the secretory phase rather than increased the intensity of the response, 0.5 mg. was used in the dog to obtain sufficient material for analysis. The secretion was collected in one hour periods for four hours, at which time the acid concentration was well in the diminishing phase. The collections were repeated on successive days and the corresponding samples pooled until sufficient material for analysis was obtained. The effect of bacterial activity was minimized by keeping the material on ice until analyzed.

The individual samples were measured and then filtered through several thicknesses of gauze. On the filtrate the free hydrochloric acid was titrated with tenth-normal sodium hydroxide, using Topfer's reagent as the indicator, and the total acidity was titrated with tenth-normal sodium hydroxide, using phenolphthalein as the indicator. The total chlorides were determined by the Harvey modification of the Volhard method. Preliminary analysis indicated that the mucin in this filtrate interfered with the direct precipitation of the various inorganic cations present. Therefore, the mucin was removed by "shaking out" with well washed chloroform. This was found to be the simplest and most satisfactory method of preparing the sample for subsequent analysis. The total base was then determined by the Fiske method; the sodium by the modified Kramer and Tisdall method on an

aliquot portion, the hydrogen-ion concentration of which had been adjusted to pH 7.1 with alcohol-washed potassium hydroxide; the potassium by the Kramer and Tisdall method on an aliquot portion, the hydrogen-ion concentration of which had been adjusted to pH 5.6 with sodium hydroxide; and the calcium by the Clark-Collip modification of the Kramer and Tisdall method on an aliquot portion, the hydrogen-ion concentration of which had been adjusted to pH 5.4 with ammonium hydroxide. Preliminary analyses revealed that magnesium was present in so small an amount, and varied so little during the gastric cycle, that it constituted a negligible fraction of the total base. Hence, it was not determined in the later experiments presented here.

Results

The determinations of five experiments are presented in the tabulation. In the first two experiments the variation of the free hydrochloric acid during the gastric secretory cycle was within normal limits. The material was obtained from two healthy laboratory workers. In the third experiment the increase in free hydrochloric acid exceeded the normal limit, and represents a curve of hyperchlorhydria. This material was collected on another occasion from the same subject as the material in the second experiment. In the fourth experiment, free hydrochloric acid was absent during all phases of the cycle and represents a curve of achlorhydria. This material was from a female patient who had diabetes of a mild degree, but who did not manifest signs or symptoms of a gastric lesion or evidence of pernicious anemia. The data of the experiment on the gastric juice from a dog with a Pavlov pouch are given in the fifth experiment. The free hydrochloric acid varied within normal limits in the uncontaminated secretion from the fundus. The data in all the experiments are similarly arranged, and all values are expressed in cubic centimeters of tenth-normal acid or base for each 100 c.c. of secretion, except the amounts of secretion which are expressed in cubic centimeters. In the preliminary analyses, the duplicate determinations of the calcium, the chloride and the acid values agreed so uniformly that the utilization of a single determination was justifiable. The sodium, the potassium and the total base were determined in duplicate, except when material was not sufficient, and their averages are presented in the tabulated experiments. The duplicate analyses agreed within a 3 per cent variation, with the exceptions indicated, and these were within a 5 per cent variation. The sum of the sodium, potassium and calcium determinations are presented as a check on the respective total base. The various inorganic constituents will be considered collectively.

In all the experiments except that with achlorhydria, the curves of the total acid and free hydrochloric acid reacted in a similar manner after stimulation by histamine. During the first part of the cycle the concentration of both increased rapidly, but in varying degrees, to a maximum which occurred thirty minutes after stimulation in the human subject, and two hours after stimulation in the dog. Toward the

end of the cycle the concentration of the total acid and free hydrochloric acid gradually decreased. In the experiment with achlorhydria (fourth experiment) stimulation caused an increase in the concentration of the total acid, which subsequently decreased, but the amount of change was so small that it was inconclusive. There was no secretion of free hydrochloric acid.

Of all the experiments the relative amount and variation in the concentration of the combined acid is striking only in the dog, in whom it constitutes 50 per cent or more of the total acid in every phase of the cycle.

The curve of secretion of chloride was comparable in all the experiments except the achlorhydria. The concentration of chloride was lowest (62 to 113 c.c. of tenth-normal solution for each 100 c.c. of secretion) in the fasting secretion. After stimulation, the concentration of chloride increased to a maximum (87 to 130), which occurred at the same time as the maximal concentration of free hydrochloric acid. Toward the end of the cycle the concentration of chloride decreased. However, the amount of increase or decrease in the chloride was in every instance less than the corresponding increase or decrease in the free hydrochloric acid. In the experiment with achlorhydria, the concentration of chloride was essentially the greatest (115) in the fasting content; it decreased after stimulation to 99. Its variations were in the same direction as the variations in the concentration of total base, but not to an equivalent amount. In comparing the relative levels of concentration of chloride in all the experiments, it would appear that the level of the concentration of chloride is dependent on the level of the concentration of the respective total cations.

The curve of the secretion of base was comparable in all experiments. The concentration of base was greatest (59 to 142 c.c. of tenth-normal base for each 100 c.c. of secretion) in the gastric content of the fasting subject. After stimulation the concentration of base decreased in each experiment to a minimum (38 to 90) which occurred approximately at the height of the acid response. Later in the cycle the concentration of base was increased. However, the amount of variation in the concentration of base was not equivalent to the respective amount of variation in free hydrochloric acid, if it was present. A comparison of the fasting levels of concentration of base in the various experiments revealed that it was greatest in achlorhydria (142) and lowest in hyperchlorhydria (59). In the mixed secretion from human subjects with a normal acidity the fasting concentration of total base (78 and 80) was slightly less than it was in the secretion from the fundus of the dog (90). It would seem that the relative concentration of total base in the fasting content was inversely proportional to the concentration of free hydrochloric acid.

Sodium was found to be the most significant of the total base cations, both in amount and in variation during the cycle. In the gastric content of the fasting human subject it comprised between 63 and 73 per cent of the total base in these experiments. In the gastric content of the fasting

dog, sodium constituted 85 per cent of the total base. After stimulation the sodium varied in the same manner as the total base, and its changes, in fact, were approximately the changes of the total base, as they constituted roughly 90 per cent of the changes in the latter.

Potassium was found to be less important in amount and in variation. In the mixed gastric content of the fasting human subject it comprised between 21 and 28 per cent of the total base. In the content of the fundus of the fasting dog it constituted only 10 per cent of the total base. Following stimulation the potassium curve differed in the various experiments. In the second, fourth and fifth experiments it varied in the same manner as the total base, but its variations, as compared with those of sodium, were much less. In the third experiment (with hyperchlorhydria) the concentration of potassium increased so that the curve was the inverse of the base curve, but its total variation was small, whereas in the first experiment, the potassium changes did not form a significant curve.

Calcium was found to be the least significant of the cations studied in these experiments. Its concentration in the content of the fasting stomach in all the experiments was approximately the same, varying from 2.9 to 3.4 c.c. After stimulation its changes in each experiment were in the same manner as the changes in the total base, but the degree of change was too small to be significant.

In comparing the concentration values of those ions common to blood serum and gastric juice it is seen that the concentration of sodium in mixed gastric juice never comes to within more than 60 per cent of its concentration in the blood serum. The concentration of calcium in a mixed gastric juice is practically the same as the concentration of the so-called diffusible calcium in blood serum, although it is less than the concentration of total calcium. On the other hand, the concentration of potassium in a mixed gastric juice is four times its concentration in serum. The concentration of chloride in a mixed gastric juice at the height of the acid secretion approaches, and in the hyperchlorhydria slightly exceeds, its concentration in blood serum. Thus, in these experiments potassium was essentially the only electrolyte that had a greater concentration in mixed gastric secretion from the human subject than in blood serum. Under these conditions it would appear that there is an active secretion of potassium into the stomach.

In figure 1 the known ions of the second experiment are plotted fractionally in an arbitrary manner. They are plotted on a line above which is acid and below which is base. The cations are in the left half and anions in the right half of the double columns. The cations are the total hydrogen ions plus the total base ions, and can be plotted accurately. The anions include the total chloride ion as determined and the unknown organic combined acid ion as titrated. The anions are arranged so that the chloride is in combination with the hydrogen of the free hydrochloric acid, when it is present. Any excess of chloride is placed in combination with the total base. When

DATA ON GASTRIC SECRETION FROM HUMAN SUBJECTS AND A DOG WITH A PAVLOV POUCH

			C.c. tenth-normal acid or base for each 100 c.c. of secretion								
		Amount, c.c.	Free hydrochloric acid	Combined acid	Total acid	Total chloride	Total base	Sum of sodium potassium and calcium	Sodium	Potassium	Calcium
First experiment, normal mixed secretion (human subject)	Fasting		0	10	10	62	79.6	79.0	56.5	19.6	2.9
	After histamine 15 minutes		10	16	26	70	63.8	68.0	44.4	21.0	2.6
	30 minutes		44	20	64	87	45.3	48.6	26.9	19.7	2.0
	45 minutes		38	14	52	79	39.2*	43.1	22.1*	18.9	2.1
	60 minutes		34	16	50	76	43.0	44.4	21.3	20.8	2.3
Second experiment, normal mixed secretion (human subject)	Fasting	16	0	18	18	62	77.5	80.0	56.7	20.8	2.5
	After histamine 15 minutes	41	45	14	59	99	57.5	56.6	33.6	20.7	2.3
	30 minutes	35	54	16	70	101	43.7	46.3	27.1	17.0	2.2
	45 minutes	41	43	15	58	93	47.5	51.9	29.7	19.8	2.4
	60 minutes	30	32	16	48	85	62.5	59.5	35.2	21.7	2.6
Third experiment, mixed secretion in hyperchlorhydria (human subject)	Fasting		37	23	60	85	58.8	59.9	39.8	17.0	3.1
	After histamine 15 minutes		44	21	65	106	61.6*	65.3	42.0	19.8	3.5
	30 minutes		85	21	106	125	37.7*			21.0	2.1
	45 minutes		78	19	97	114	38.8	41.4	20.0**	19.4	2.0
	60 minutes		46	15	61	89	45.6	47.6	26.3	18.4	2.9

Fourth experiment, mixed secretion in achlorhydria (human subject)	Fasting	35	0	5	5	115	142.5	124.1	90.5	30.0	3.6
	After histamine 15 minutes	38	0	7	7	118	127.5	124.7	96.3	25.3	3.1
	30 minutes	40	0	7	7	104	103.7	101.1	72.7	25.4	3.0
	45 minutes	32	0	5	5	99	90.0	98.2	70.7	24.3	3.2
	60 minutes	30	0	5	5	107	107.5	112.0	80.5*	28.3	3.2
Fifth experiment, secretion from fundus (normal dog)	Fasting		19	61	80	113	90.0**	97.0	82.0	11.6	3.4
	After histamine 1 hour		52	62	114	130	75.0	77.4	64.6	9.4	3.4
	2 hours		56	56	112	130	61.0	66.1	53.5	9.2	3.4
	3 hours		32	63	95	124	85.0*		73.7*		
	4 hours		12	74	86	121	97.0*	96.3	81.9*	10.4*	4.0
Blood serum values						120	160.0		150.0	5.0	5.0

*Single determination only

**Duplicates within 5 per cent variation

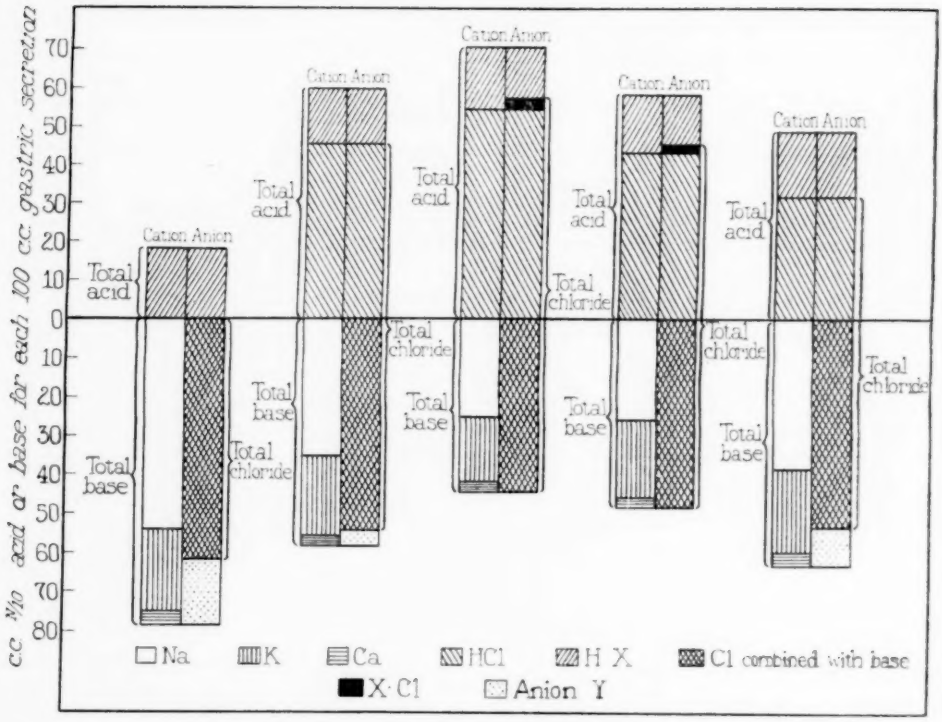

FIG. 1. Data of the second experiment. The blocks from left to right are the successive phases of the secretory cycle. The first represents the fasting secretion, and the next four represent the successive fifteen-minute intervals after histamine stimulation. Na, K, and Ca are the cations of the total base. H-X is the combined acid as determined by the difference between the titration with phenolphthalein and the titration with Topfer's reagent. X represents the unknown anion of the combined acid. HCL is the free hydrochloric acid, determined by titration with Topfer's reagent. Cl combined with base is shown as the difference between the total chloride and the chloride combined in free hydrochloric acid. Anion Y is an undetermined anion and is the difference between the total base and the chloride in combination with base. X-Cl is the chloride which exceeds the equivalent of the sum of the total base and the free hydrochloric acid, and is shown in combination with combined acid.

there is more chloride than the sum of that combined with free hydrochloric acid and with total base, it is placed in combination with the combined acid anion. When the sum of the free hydrochloric acid and the total base is greater than the total chloride, the excess of base is combined with an undetermined anion. This anion may possibly be sulphate, phosphate, carbonate, proteinate or an organic anion. At the height of normal gastric secretion the difference between the total cations (hydrogen and base) and the measured anions (total chloride and combined acid anion) is between plus or minus 3.5 c.c. of tenth-normal solution for each 100 c.c. of the mixed secretion. This is a value which is well within the limits of the experimental errors of the various analytical method. During the fasting period the undetermined anion in combination with base (anion Y) is

relatively larger in amount (15.5 c.c. of tenth-normal solution for each 100 c.c.) and is greater than the summation of probable experimental errors. At the end of the cycle the fasting state is approached. This would seem to indicate that after stimulation in the normal stomach, anions other than chloride ions were not present, except the unknown organic anion in combination with combined acid, whereas they are present in the fasting secretion.

Comment

All observers agree, in the main, as to the changes in the concentration of the free hydrochloric acid and the total acid of gastric juice that occur after gastric stimulation. Dobson, Polland, Roberts and Bloomfield, and Close found that the maximal concentration of free hydrochloric acid occurs about thirty minutes after stimulation with histamine in 0.1 mg. doses, except in cases of true achlorhydria. Dobson and Close showed that larger doses of histamine prolonged the secretory response rather than increasing its intensity. These observations have been substantiated in the experiments reported here.

However, the changes in the concentration of total chlorides after stimulation have not been found to be the same by various observers, as has been pointed out. In all the experiments, except the achlorhydria, the concentration of total chloride definitely increased after gastric stimulation to a maximum which occurred at the same time as the maximal concentration of free hydrochloric acid, and then decreased as the concentration of acid decreased. In all instances the concentration of chloride exceeded the concentration of free hydrochloric acid, which would indicate that chloride is secreted into the stomach in forms other than hydrochloric acid. In the experiment with achlorhydria the concentration of chloride decreased; its variations roughly paralleled the variation in the concentration of sodium.

The values for concentration of total base in these experiments have been presented. With one exception, they are in accord with the observations on the fractional curve of Polland, Roberts and Bloomfield, and Close. Whereas Close found an increase in the concentration of base after stimulation in four cases of achlorhydria, I found a definite decrease in the case which I observed. Following the report of Polland, Roberts and Bloomfield, I attempted, in two experiments, to recover all the gastric juice secreted in each period of the gastric cycle (second and fourth experiments). The calculated total output of base in the normal secretion of the human subject during the gastric cycle in the second experiment gave a curve which approached theirs. In the fasting period 16 c.c. of secretion was recovered, and in the four successive fifteen-minute periods after stimulation by histamine, 41, 35, 41, and 30 c.c. of secretion were recovered respectively. This gave a total amount of 12.4 c.c. of tenth-normal base in the fasting content, and 23.6, 15.3, 19.5 and 18.8 c.c. of tenth-normal base in the successive periods of the gastric cycle after stimulation. That only 35 c.c. of secretion was recovered at the height of the acid curve (that is,

in the second fifteen-minute period) probably accounts for the observation that the maximal output of base did not attend the maximal output of acid. This was probably due to failure to recover the entire secretion in that period. It gives a clear indication of the error which such a failure would induce, and shows that the procedure at best has its pitfalls. However, it is fairly definite in this experiment that there is an actual increase in the output of total base after stimulation. In the case of achlorhydria (fourth experiment), the volume of secretion formed a more uniform curve. In the fasting period 35 c.c. of secretion was recovered and after stimulation by histamine 38, 40, 32, and 30 c.c. of secretion were recovered in the respective fifteen-minute periods. The total output of base in the respective periods was 49.9, 48.5, 41.5, 38.8, and 32.3 c.c. of tenth-normal base. Thus, in the experiment with achlorhydria, the total output of base as well as the concentration of base was decreased after stimulation by histamine. The significance of this observation is still obscure.

Complete fractionation of the total base in gastric secretion, during the successive phases after stimulation, seemingly has not been reported heretofore. The values for concentration of sodium, potassium and calcium during the gastric cycle have been given. When calculated in actual amount of each that are secreted in the second and fourth experiments, they are found to vary in the same manner as the total base in their respective experiments. The sodium has been accurately determined and in these experiments it is unquestionably the most significant of the gastric bases. Potassium is second in importance, whereas calcium is relatively of no significance, and magnesium may be disregarded.

Various workers have calculated the unknown amount of various electrolytes from the determined values of other electrolytes. After Gamble and McIver determined the phosphate and protein in samples of gastric juice and found them in negligible amounts as compared with the chloride anion, they believed that the concentration of hydrogen ions is approximately equal to the difference between the chloride ion and the fixed base. This was found to be true in the experiments reported here. Berglund, Wahlquist and Sherwood found that after stimulation the total chloride corresponded approximately to the hydrochloric acid titrated. This was not found to be true in my experiments. Polland, Roberts and Bloomfield compared the determined gastric acidity with the acidity as calculated by subtracting the base from the total chloride. They found the determined free hydrochloric acid to be greater than the calculated free hydrochloric acid in the fasting content, and attributed this to the absence of free hydrochloric acid. After stimulation the calculated free hydrochloric acid was uniformly higher than the determined free hydrochloric acid, the difference between them not being completely accounted for by base, although the discrepancy was not great.

This is essentially a statement that in the fasting content there is an excess of base over the chloride combined with base, and would indicate

that an anion other than chloride is in combination with base. After stimulation there is not enough chloride to account for both the free hydrochloric acid and the base although the discrepancy is not large, and would indicate that the base is entirely combined with chloride. This was found to be essentially true in these experiments. Close calculated the amount of base chloride by subtracting the total acid from the total chloride and found that its concentration was greater in the fasting content than at the height of the secretory response. This calculation is made but I have calculated the base chloride as the difference between the total chloride and the free hydrochloric acid.

SUMMARY

Determinations of the acid-base composition of gastric juice during the secretory cycle in human beings and in one dog have been presented. Data from subjects illustrative of the changes in normal, hyperchlorhydric, and achlorhydric states have been given.

The concentration of chloride was found to be increased after stimulation except in the achlorhydric state, but in amounts which were less than the increase in the concentration of free hydrochloric acid.

During the secretory cycle the concentration of base varied inversely to the concentration of acid.

Sodium was found to be the most significant of the individual bases, both in regard to its amount, and in regard to its relationship to the variation in the total base during the secretory cycle.

The concentration of the determined ions was found to be less in the stomach than in blood serum, with the exception of potassium. The concentration of potassium was from three to five times greater in the gastric juice than in the blood serum.

BIBLIOGRAPHY

[1]BERGLUND, HILDING, WAHLQUIST, HAROLD AND SHERWOOD, K. K.: Hydrochloric acid and total chlorine content of pure gastric juice produced after histamine injection. Proc. Soc. Exper. Biol. and Med., 1927, xxiv, 927-929.

[2]BULGER, H. A. AND ALLEN, D. S.: Studies on the mechanism of gastric hydrochloric acid secretion. Proc. Soc. Exper Biol. and Med., 1927, xxiv, 902-903.

[3]BULGER, H. A., STROUD, C. M. AND HEIDEMAN, M. L.: Studies of the chemical mechanism of hydrochloric acid secretion. I. Electrolyte variations in human gastric juice. Jour. Clin. Investigation, 1928, v, 547-560.

[4]CLOSE, KATHERINE M.: Total base in gastric contents and gastric secretion. Ann. Int. Med., 1929, ii, 1185-1193.

[5]DOBSON, H. V.: The quantitative determination of gastric secretion. (Unpublished data.)

[6]GAMBLE, J. L. AND MCIVER, M. A.: Fixed base in gastric juice. Proc. Soc. Exper. Biol. and Med., 1926, xxiii, 439-448; The acid-base composition of gastric secretions. Jour. Exper. Med., 1928, xlviii, 837-847.

[7]POLLAND, W. C., ROBERTS, A. M. AND BLOOMFIELD, A. L.: The chloride, base and nitrogen content of gastric juice after histamine stimulation. Jour. Clin. Investigation, 1928, v, 611-637.

[8]ROSEMANN, R.: Beiträge zur Physiologie der Verdauung. Arch. f. d. ges. Physiol., 1907, cxviii, 467-524.

Hay Fever

Its Control Through Efferent Interception

By Hiram Byrd, M.D., *Detroit Michigan**

HAY fever, whether seasonal or non-seasonal, is defined in this connection in terms of excess sneezing. Now a sneeze has its conscious origin in the roof of the nose, in a region which without any attempted delineation, may be designated as the "sneeze region."

This sneeze region receives its nerve supply from two branches of the trigeminal—from the superior maxillary, via Meckel's ganglion; and from the ophthalmic, via the nasal nerve. Therefore efferent impulses routed down the trigeminal nerve may reach the sneeze region via either the ophthalmic or the superior maxillary. And since this may occur on either side without involving the other, it is obvious that *there are four routes via which such efferent impulses may reach the sneeze region.*

As will be shown later, there are ample grounds for formulating the hypothesis that the *sneezes are engendered by efferent impulses in excess.* Now if sneezing is engendered by efferent impulses, registering in the sneeze region, then it is obvious that intercepting these impulses before they reach the sneeze region will effectively prevent the sneezing. Such interception may be accomplished by anesthetizing the nerves proximal to the sneeze region, which intercepts the passage of nerve impulses or currents temporarily; or by injecting the nerves with alcohol, which interferes with the passing of currents more or less permanently.

Now efferent impulses* routed to the sneeze region via the ophthalmic nerve have to pass the *nasal nerve;* and those routed via the superior maxillary have to pass *Meckel's ganglion,* at which loci the nerves are anatomically reachable. Therefore, the interception of such currents by anesthetization, or injection, is not an important procedure.

Here then the stage is all set for testing the hypothesis under the most rigidly controlled conditions. For if it be true that excess sneezing is engendered by efferent impulses routed down these four nerves in excess quantum, then all one has to do to arrest the sneezing, *regardless of its antecedent cause,* is to obstruct the four paths of impulses into the sneeze region, which may be done by inject-

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*It is to be noted that physiology assigns to the maxillary and ophthalmic branches of the trigeminal nerve an exclusively sensory function—an assignment that, in the light of these disclosures, calls for re-examination.

ing the two nasal nerves, and the two Meckel's ganglia, with alcohol.

Such injection, moreover, if followed by relief from the sneezing, not only supports the hypothesis, but *provides a ready therapeutic approach for the practical control of hay fever.*

It was Sluder who first noted that injecting Meckel's ganglia with alcohol arrests some cases of hay fever but not all. Subsequently one of his followers reported some 43 cases in which he had injected Meckel's ganglia for hay fever, with results ranging all the way from complete and permanent relief on the one hand to little or no benefit on the other. The writer's experience is in harmony with those that have found their way into the literature. In some instances, injecting Meckel's ganglia with alcohol gives immediate, complete, and permanent relief from hay fever. In other instances, the relief is only partial, or absent entirely.

In view of the foregoing consideration, however, this is exactly what is to be expected. For while injecting Meckel's ganglia intercepts impulses routed to the sneeze region via the superior maxillary, it leaves those routed via the ophthalmic nerve quite unobstructed, so as only partially to fulfill the conditions for testing the hypothesis.

It was subsequently noted that hay fever cases who had experienced partial but not complete relief from injecting Meckel's ganglia, uniformly exhibited a distinct rhinitis in the anterior portion of the nasal chambers corresponding to the region of distribution of the nasal nerves. Sometimes this anterior rhinitis, it was noted, was limited to one side, and in such cases, it was further noted, the sneezes had their conscious origin in the affected side. The thought was compelling that in these cases, after Meckel's ganglia had been injected, there was still quite a sufficiency of current coming down the nasal nerve to continue the symptoms. Thus, in order to fully test the hypothesis, we were face to face with the problem of injecting the nasal nerves.

The nasal nerves, however, so far as the writer was able to find, had never been injected with alcohol. And since such injection would have to be made in such close proximity to the cribriform plate, and the olfactory distribution, it was not undertaken without due consideration.

In the meantime another device was resorted to. A case presented in the person of a nurse who had had non-seasonal hay fever from childhood with seasonal exacerbations. Meckel's ganglia were injected as the first step. This was found to give ten days' relief, after which the sneezing returned, though somewhat modified in severity. Moreover, the conscious origin of the sneeze now appeared to be limited to one side.

The region of the nasal nerve on that side was now cauterized with 40% solution of silver nitrate. While this had the effect of arresting the sneezing, the line of approach was too severe, and was accordingly abandoned.

A case now presented with non-seasonal hay fever of three years' duration—a very aggravated case. Meckel's ganglia were injected as the first step, whereupon the hay fever ceased for a period of twenty days, and when it re-

turned, as in the preceding case, the conscious origin of the sneezes appeared to be limited to one side.

It was now decided to undertake the injection of the nasal ** nerve of this side with alcohol. To this end an applicator was passed into the region, and X-rayed in place, so as to serve as a guide in finding one's way. With these precautions, the injection was made, with the result that all symptoms of hay fever were immediately arrested. Nor had there been any recurrence at last accounts, some fifteen months afterward.

In this test then, which has since been verified in both seasonal and nonseasonal hay fever, all evidence goes to support the hypothesis that whatever the antecedent cause of the sneeze may be, its immediate cause is something that travels along the nerves, and which does not have the power to pass a section that is anesthetized or injected with alcohol.

But associated with the sneezes of hay fever are other symptoms, as weeping of the nose and eyes, and particularly burning and itching of the eyes. These associate symptoms are uniformly arrested simultaneously with the sneezing; so that the evidence that goes to establish efferent impulses as an obligate factor in sneezing, similarly establishes such impulses as an obligate factor in the associate symptoms. Here then we must conclude that not only the sneezing, but the whole train of associate symptoms, with or without the sneezing, is similarly engendered by excess efferent impulses, and subject to the same methods of control. Let us now see what evidence we have that these associate symptoms, when they appear as entities apart from hay fever, come under the same control.

A case of seasonal itching and burning of the eyes, very similar to that associated with hay fever, but without the sneezing, was found to be temporarily arrestible by anesthetizing Meckel's ganglia. This procedure was repeated several times, with uniform results, but the symptom persistently returned. At length the ganglia were injected with alcohol under general anesthesia. The patient awoke free from the eye distress, which at last accounts had never returned.

Similarly, an aggravated case of rhinorrhea, but without sneezing, presented for treatment. It was found that anesthetizing Meckel's ganglia gave temporary relief from the rhinorrhea, whereupon the ganglia were injected with alcohol. This gave complete relief for a few days, after which the rhinorrhea returned, but limited to the left side, and to the anterior portion of the nose. The left nasal nerve was now injected with alcohol, whereupon the rhinorrhea ceased altogether.

Again, a case of enlarged tonsils, hypertrophic turbinates, and "red-nose," but without sneezing, presented for treatment. It was elected to inject Meckel's ganglion on one side, leaving

**Later developments have disclosed that injecting the nasal nerves at a more proximal point, that is through the orbit, at the point just proximal to the anterior ethmoidal foramen, is a much more dynamic procedure, and is, in itself, often quite sufficient to relieve the hay fever or hyperesthetic rhinitis without recourse to injecting the sphenopalatine ganglia.

the other for control purposes. Following the injection the tonsil on the injected side shrank to half the size of its fellow; the turbinates on that side underwent pronounced regression, and that side of the nose assumed its normal color and texture, while conditions on the opposite side remained unchanged.

Thus would it seem that the sneezing and the other symptoms associated with hay fever are so many separate entities, but all underlaid with the same actuating cause, and all amenable to the same therapeutic approach—intercepting the passage of efferent currents into the affected loci.

Re-classifying these several symptoms, the evidence is that efferent impulses in excess quantum engender:

"Sensory dys-functions," as the itching and burning of the eyes;

"Motor dys-function," as the muscular activity involved in the act of sneezing;

"Respiratory dys-functions," as the sneeze itself; and

"Secretory dys-functions," as the rhinorrhea and the lachrymation.

Moreover, and this is important, it is only a step from itching of the eyes to itching of the ears, to pruritus vulvae, and to other sensory manifestations, as arthritis, lumbago, gout, sciatica, etc., all of which have been repeatedly relieved by anesthetizing the nerves along the intervening efferent path. It is only a step from the motor dysfunction involved in the act of sneezing to the motor dys-functions of chorea, and these too have been immediately and repeatedly relieved by anesthetizing the nerves along the intervening efferent path. It is only a step from hay fever to asthma, and that too has similarly been relieved. Finally it is only a step from the secretory dys-functions involved in the rhinorrhea and lachrymation of hay fever to the secretory dys-function involved in diarrhea, and that too has been immediately relieved by anesthetizing the intervening efferent path.

So we must conclude that the arrest of sensory, motor, respiratory, and secretory dys-functions in connection with hay fever, by intercepting the efferent impulses, *involves nothing unique, or restricted to hay fever phenomena, but is indeed merely a part of an underlying principle universal throughout the body.*

Let us now see how far physiology has gone to disclose such a principle. In his recent annual address, Sir Arthur Lovatt Evans, president of the section of physiology of the British Association for the Advancement of Science, said:

> "A state of disease is never a thing in itself but is always a quantitative change in some physiological process, an increase or diminution of something that was there to begin with."

We have it from eminent physiological authority that efferent currents serve to "motivate and stabilize" the various physiological functions. In other words the efferent currents constitute a sort of super-function.

It seems a necessary deduction that there must be limits beyond which the quantitative variations of this super-function cannot go without causing disruption in the functions it normally motivates and stabilizes. This would seem to postulate that efferent cur-

rents in excess quantum may cause various and remote dys-functions, and that these dys-functions may be arrested by the interception of such currents at any locus along their path.

We may now inquire of physiology, is it experimentally known that nerve impulses, or currents, may engender remote dys-functions? and that such dys-functions may be arrested by intercepting the passage of these currents?

Recently the writer was visiting the physiological laboratory of one of the great institutions of the Middle West. On this particular occasion the experimenter had the vidian nerve of a narcotized animal exposed, to which he was applying a stimulus, and noting the results. When the stimulus was applied the respiration, the heart action, and the blood pressure became quite disturbed. When it was withdrawn, these disturbances would subside.

Subsequently the writer wrote to the Director and the Assistant-Director of these laboratories, referring to the incident in the following language:

> "As I understand . . . the electrode applied to the nerve caused an impulse, (or succession of impulses, or current or *something,*) to travel along the nerve to some remote locus and *cause* these symptoms. Without raising the question as to the nature of the thing that travels along the nerve, (current, let us call it,) or the mechanism of how it travels, or the mechanism of how it causes these disturbances, or even where it operates to cause them, can't we consider this *current* in its bare essentials as follows: As originating at the locus of stimulation, as traveling along the nerves, as causing these remote disturbances, and as being unable to pass a section of nerve that is anesthetized, frozen, or injected with alcohol?"

To this question the Director and the Assistant-Director answered separately: "Yes."

Having seen that the initiation of remote dys-functions by means of nerve currents is commonplace in the physiological laboratory, let us inquire what evidence the clinic affords on whether the efferent nerve currents of the organism in excess quantum may similarly cause remote dys-functions.

The anatomies show us that Meckel's ganglion is the most important isthmus connecting the largest cranial nerve (the trigeminal) with the sympathetic system. If excess efferent impulses cause remote dys-functions, then in cases where these excess impulses are routed adown the trigeminal nerve and across this isthmus to the sympathetic system, it should be possible, by anesthetization of this isthmus, or injection of it with alcohol, to arrest such dys-functions in regions *distal* to the isthmus, but in no case should it be possible to arrest dys-functions by this procedure in regions of distribution *proximal* to the isthmus.

Now this has actually proven to be the case. Although in more than five hundred cases have remote dys-functions been arrested by anesthetization of Meckel's ganglion in regions distal to it, not one has been found arrestible in regions of distribution proximal to

the ganglion. Thus, upon the hypothesis that efferent currents in excess quantum were the immediate cause of the various dys-functions arrested, the expectations postulated from the anatomical framework are fulfilled in minutest detail.

It may be added that the list of dys-functions thus intercepted includes not merely subjective, but objective disturbances, so that we do not have to rely upon the patient's testimony alone that the symptom has abated. Indeed this fact, together with the immediateness and decisiveness of these reactions, when positive, gives such clinical observations an accuracy comparable only to the controlled experiments of the laboratory.

In summary, the hypothesis that efferent currents in excess quantum are the determining factor, not only in sneezing, but in the other dys-functions associated with hay fever, and indeed with sensory, motor, respiratory, circulatory, and secretory dys-functions throughout the body, is seen to provide us with an interpretation that is at once in harmony with Evans' law, and with the experiments of the physiological laboratory, and with the anatomy of the structures concerned.

Moreover, this hypothesis, together with the already developed methods of intercepting nerve currents, provides clinical medicine with an instrument of precision in research comparable to the microscope and the test tube in their respective fields—provides a method of investigating sensory phenomena, thus opening to clinical medicine a field of research which, by its very nature, is excluded from the physiological laboratory, where the experimental subject is a dumb narcotized animal.

Moreover *the hypothesis that efferent impulses or currents in excess quantum cause remote dys-functions*, provides a thought formula which, so far, has served as an unerring guide in predicating what may be expected in untried situations. And growing out of this, the principle of *efferent interception* provides a therapeutic approach that has already proven of great value in a number of fields, while it may be said to have brought hay fever and vasomotor rhinitis definitely under medical control.

Pioneer Medicine—Dr. Joseph O'Dwyer and Dr. Wm. Dunlop*

By J. W. Crane, *University of Western Ontario Medical School, London, Ontario*

One of the fascinations in studying pioneer life is the discovery in unexpected places of some reminder of the doctor who had in his day contributed abundantly to the health and happiness of his community. The chicken coop may be a storehouse for such finds (Fig. 1.) A pair of saddle bags brought to Ontario from the New England States by a United Empire Loyalist doctor was found covered with hay in the manger of an unused barn.

The University of Western Ontario was most fortunate in securing Dr. Joseph O'Dwyer's surgical bag containing several types of intubation tubes, some gold-plated, others of hard rubber, a mouth gag covered in part with chamois for protection of the gums of infants, ice cap, a partially used tube of lubricant and a reel of silk thread. (Fig. 2, Fig. 3.) These treasures were rescued when one of his relatives living near London was making her annual domestic disturbance—popularly known as spring housecleaning. The attic at such times always furnishes fuel for the fire.

O'Dwyer, who began the study of medicine in London, Canada, can hardly be called a pioneer physician, except in the sense that he was a pioneer in devising an efficient intubation tube. Like other benefactors of mankind he was ridiculed, and suffered severely because of his sensitive nature. When he described his invention at a meeting of the New York Academy of Medicine, he was told he was either a knave or a fool. Poor O'Dwyer went home to bed, and stayed there for three days, not wishing to see anybody.

The more time one devotes to the study of the lives of the doctors who were "guide, philosopher and friend" to the pioneers of this country, the more one is convinced that their lives were characterized by sturdy heroism and self-sacrifice in doing the routine of their everyday life. There have been countless Dr. Maclure's among them. The vast majority have gone to their graves "unknown, unknelled and unsung." Admiration for such noble men arouses a hope that some permanent recognition be given them. A small museum in every county could be made the storehouse for the instruments, prescription books, diplomas, professional correspondence, and other

*Read before the American College of Physicians, Annual Clinical Week, April 12, 1929, Boston.

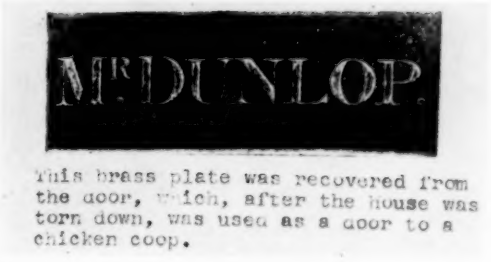
MR DUNLOP.
This brass plate was recovered from the door, which, after the house was torn down, was used as a door to a chicken coop.

FIG. 1.

FIG. 2.

FIG. 1. Surgeons in England receive at graduation the degree of Bachelor or Master of Surgery and are addressed as Mr.. A physician receives an M.D. degree and is known as Doctor.

FIG. 2. Dr. O'Dwyer spent one year in the office of Dr. Anderson, London, Ont., later going to New York.

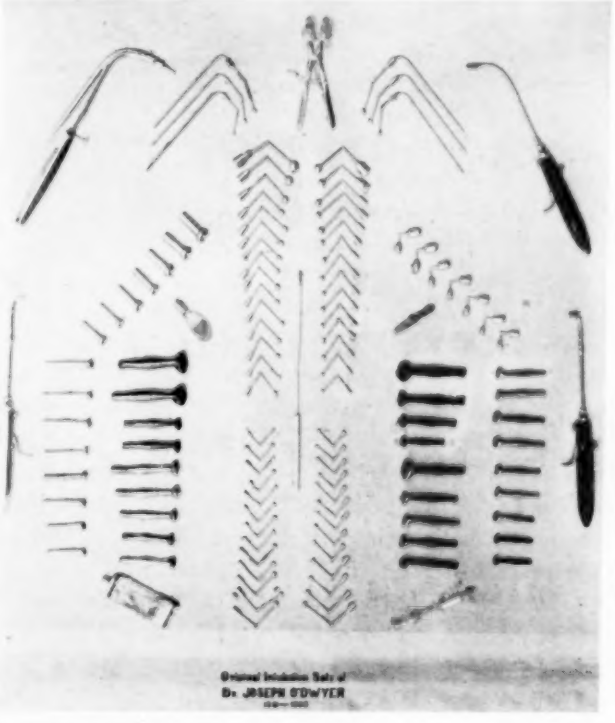

FIG. 3. O'Dwyer's intubation of various sizes, his reel of silk, partially used tube of lubricant, mouth gag with jaws covered with chamois, intubator and extubator.

interesting objects associated with the physicians of that community. Such material will be invaluable when the history of medicine on this continent is written, and unless an immediate effort is made to collect and preserve such mementos, the future historian will be woefully handicapped.

Dr. W. Dunlop (1792-1848)

Last century, Dr. William Dunlop, a Scotchman, was one of the outstanding figures in the settlement of Western Ontario, especially that part known as the Huron Tract—the district lying between Toronto and Lake Huron. Physically he was well adapted to the pioneer life, in that he was built on generous lines. He stood six feet three inches in his stockings and measured two feet eight inches across the shoulder. "The fur," the term used by one writer in referring to his hair, "is the genuine Caledonian redness and roughness, and the hide from long exposure to Eurus and Boreas has acquired such a firmness of texture that he shaves with a brickbat." He was popularly known as "Tiger Dunlop," because, while in India, he had cleared two or three islands in the Ganges of man-eating tigers. He received his education, literary, medical and convivial, in Glasgow. The illustration (Fig. 4) shows a few of the twelve decanters, which he kept filled with different brands of alcoholic stimulants and which were named after the twelve apostles. His convivial propensities are reflected also in his last will and testament, a copy of which will be referred to later.

He was the author of a small octavo entitled "Recollections of the American War" in which he gives a breezy and vivid description of the American War. In July, 1814, he was sent to

Fig. 4. Dr. Dunlop, (1798-1848) or "Tiger" Dunlop. He named the twelve decanters after the twelve aposles.

Butler's Barracks, at Niagara, and arrived the day following the engagement at Lundy's Lane.

"Waggon after waggon arrived," he tells us, "and before midday I found myself in charge of 220 wounded, with no one to assist me but my hospital sergeant who, luckily for me, was a man of sound sense and experience. The charge was too much for us and many a poor fellow had to submit to an amputation whose limb might have been preserved had there been only time to take reasonable care of it. But under the circumstances it was necessary to convert a troublesome wound into a simple one, or to lose the patient's life from want of time to pay him proper attention. I never underwent such fatigue as I did for the

first week at Butler's Barracks. The weather was intensely hot, the flies were in myriads and lighting on the wounds deposited their eggs, so that maggots were bred in a few hours,* so that, long before I could go round dressing the patients it was necessary to begin again. For two days and two nights I never sat down. On the morning of the third day I fell asleep on my feet."

Although as a surgeon he was supposed to be a non-combatant, still he was often found in the firing line. One incident illustrates the kindness and courage of Dunlop, who at this time was only 22 years of age. He carried several of the wounded to safety, but one of them was a corpse when he reached the hospital quarters, having received a second bullet in transit.

There was urgent need during the following winter for supplies for the garrison at Mackinaw in case of siege, necessitating the building of a road from Lake Simcoe to Penetanguishene, a distance of 30 miles. Dunlop agreed to engineer the construction of this road through a dense forest with snow four to six feet deep. Bridges had to be thrown across streams, requiring men to stand in ice-cold water up to the middle. Oxen were the only method of transport. Against such odds he was able to accomplish what was regarded as the impossible, and completed the work in an incredibly short time, but much to his chagrin, peace was declared just as the road was finished.

One night while building this road, he lost the trail in the bush and had to sleep out all night with the temperature below zero. Knowing too well the action of alcohol when taken internally under such circumstances, he poured the rum into his boots instead of into his stomach. He made a hole in a snow bank, crawled in, placed his little dog on top of him, and went to sleep. In the morning the dog was dead, his toes frozen and his hands numb, but he was able to make his way to the camp. He recovered completely in three weeks under the care of a French-Canadian who "enveloped his feet in a poultice of boiled beech leaves." Dunlop thought at that time that this was the only instance of a white man sleeping out in a Canadian winter night, without fire or covering of any kind.

At the close of the American War, his regiment was ordered to England, arriving too late to participate in the Battle of Waterloo. Dunlop, however, followed his regiment to India. He developed jungle fever and was invalided to England. His restless activity found an outlet in editing newspapers, writing articles for Blackwood's, founding a club with the euphonious name of "The Whistle and the Pig," floating industrial companies, and finally as Lecturer in Medical Jurisprudence at the University of Edinburgh. His lectures are referred to as a mixture of fun and learning, law and science blended with rough jokes and anecdotes not at all of the most prudish nature. He edited an edition of Beck's Medical Jurispru-

*Dr. W. S. Baer of Baltimore has recently reported the successful treatment of cases of chronic osteomyelitis by applying living maggots to the wound.

dence, a book that is highly entertaining as well as instructive.

As a result of a love affair, Dunlop left for Canada, having accepted the position of Warden of the Forest for the Canada Company. In 1826 he arrived in Goderich on Lake Huron and made this place his headquarters for the next eighteen years. He was joined later by his brother, Captain Robert Dunlop, of the Royal Navy, and they had as their housekeeper, Lou McColl—a very efficient and resourceful woman. Dr. Dunlop threw all his energy in securing settlers for this part of Ontario. His book, "Statistical Studies of Upper Canada," published in 1833, is filled with enthusiasm and optimism and, undoubtedly, influenced many immigrants to locate in his district. In 1841 he was elected a member of Parliament, and continued to represent the Huron District until 1846, when he accepted a government position on the Lachine Canal near Montreal. He died in 1848 at Lake Louise, near Montreal, and faithful Lou brought his body to Goderich for burial. He asked her "to put his back up against that of his brother, in order to keep him warm." A cairn has been erected over the graves of these two remarkable pioneers on the Maitland River overlooking Goderich. (Fig. 5.)

Records are available regarding his professional work, but these are not as appealing as those dealing with his social and convivial activities. His method of liquifying the debt owed by the brothers to their housekeeper Lou is not original but is characteristic of his initiative in solving difficult

Fig. 5. Cairn of Dr. Dunlop on the Maitland River overlooking Goderich.

problems. The brothers held a council of war, and it was agreed that matrimony was the logical solution,—but who was to marry Lou? To settle the question the doctor suggested that it be left to a flip of a coin. He happened to have a double-headed penny, with the result that the Captain won the toss and a wife. Lou was consulted, and proved quite agreeable to the settlement. She and the Captain were married, although it has been said that Lou had a stronger attachment to "the dear doctor" than to her own husband.

Dunlop's Will

Dr. Dunlop's will is a classic in Canadian forensic history. It reads as follows:

"In the name of God. Amen. I, William Dunlop, of Gairbraid, in the township of Colborne, County and District of Huron, Western Canada, Esquire, being in sound health of body, and my mind just as usual, which my friends who flatter me say is no great shakes at the best of time, do make this my last will and testament as follows—revoking, of course, all former wills:

"I leave the property of Gairbraid and all other landed property I may die possessed of, to my sisters, Ellen Boyle Story, and Elizabeth Boyle Dunlop, the former because she is married to a minister whom (God help him!) she henpecks: the latter, because she is married to nobody, nor is she likely to be, for she is an old maid and not market-rife; and also I leave to them and their heirs my share of the stock and implements on the farm, provided always that the enclosure round my brother's grave be reserved, and if either should die without issue then the other to inherit the whole.

"I leave to my sister-in-law, Louisa Dunlop, all my share of the household furniture and such traps with the exceptions hereinafter mentioned.

"I leave my silver tankard to the oldest son of old John, as the representative of the family; I would have left it to old John himself, but he would melt it down to make temperance medals, and that would be a sacrilege—however, I leave my big horn snuff-box to him, he can only temperance horn-spoons of that.

"I leave my sister Jenny my Bible, the property formerly of my great-great-grandmother, Bethia Hamilton, of Woodhall, and when she knows as much of the spirit of it as she does of the letter, she will be another guise-Christian than she is.

"I also leave my late brother's watch to my brother Sandy, exhorting him at the same time to give up wiggery, radicalism, and all other sins that do most easily beset him.

"I leave my brother Alan, my big silver snuff-box, as I am informed he is rather a decent Christian, with a swag belly and a jolly face.

"I leave Parson Chevasse (Maggie's husband) the snuff-box I got from the Sarnia Militia, as a small token of my gratitude for the service he has done the family in taking a sister that no man of taste would have taken.

"I leave John Caddle a silver teapot, to the end that he may drink tea therefrom to comfort him under the affliction of a slatternly wife.

"I give my silver cup with a sovereign in it to my sister, Janet Graham

Dunlop, because she is an old maid and pious, and therefore will necessarily take to horning, and also my gramma's snuffmull, as it looks decent to see an old woman taking snuff."

This short sketch of Dr. Dunlop is evidence that the lives of the early physicians can fulfill the requirements needed to make this form of historical research a hobby of the practicing physician. Let him secure as a beginning the details of the medical history of his own community. He will then see the necessity of placing in a fireproof building such material as surgical instruments, saddle bags, diplomas and professional correspondence. If such is not feasible, it might be well to resurrect the Egyptian form of burial. Let us bury with our dead everything that may be of historical value in the future. Graves then will be as much sought after as that of King Tut.

REFERENCES

LIZARS, ROBINA AND KATHLEEN MACFARLANE: In the Days of Canada Company, Toronto, 1896.

CANNIFF, WILLIAM: The Medical Profession in Upper Canada, pp. 352-362, Toronto, 1894.

DUNLOP, ARCHIBALD: Dunlop of that Ilk, pp. 46-62, 1898.

MACLISE: Gallery of Illustrious Literary Men.

Editorials

*HOW THE SCARLET FEVER EPIDEMIC AT BEREA COLLEGE WAS CONTROLLED**

Nothing can more strikingly illustrate the fact of the great advance in our knowledge of scarlet fever than the story of the successful management of the important epidemic of this disease occurring at Berea College, last spring. The story of the control program carried out there, based upon the newer knowledge of scarlet fever, its etiology and prevention, is of such significance in the practice of medicine, that it is considered to be well worth while to tell it again here, in the hope that it may reach some of those practitioners who might otherwise miss the local reports of the Berea epidemic. Berea College is located in Berea, Kentucky, an agricultural community with a population of about 1,600. The college students, faculty and workers number about 2,200. Most of the workers, part of the faculty and about 100 students live off of the campus. The others live in various campus dormitories. The students are largely drawn from the mountain sections of Kentucky and the surrounding states. Two large boarding halls, each with its own kitchen and several dining rooms, are maintained for students. The school has an independent water supply, provided through an impounding reservoir. The milk supply is largely from the college herd, and up to the time of the epidemic was being used raw. A small amount of raw milk obtained from the outside is pasteurized at the college. The college hospital, with its isolation annex for communicable diseases, cares for sick students. Medical service is provided by a staff of three physicians. During February and the early part of March, there were 12 students with scarlet fever admitted to the college hospital. All of these patients had a characteristic scarlatinal rash followed by desquamation. Later on it became apparent, on questioning the student body, that there were many mild, unrecognized cases of sore throat, associated in a majority of instances with headache, and either nausea or vomiting, or both. A few of these students had reported at the out-patient clinic for treatment, but in the absence of a recognizable rash at the time they were seen, the condition was throught to be tonsillitis. On March 11 one case only of scarlet fever was admitted to the college hospital, but on March 12, there were 94 admissions, each case having sore throat, headache, malaise and some

*A Practical Demonstration in the Control of Scarlet Fever. By J. L. Jones, M.D., State Epidemiologist, Louisville, and John W. Armstrong, M.D., Physician and Health Officer, Berea College, Berea (Kentucky Medical Journal, November, 1929).

degree of fever. All throats had a similar appearance, scarlet arch of fauces and an exudate over the tonsils. The State Board of Health was at once notified, and its representatives in connection with the College Medical Staff immediately began an investigation. On March 13, 80 more similar cases were admitted to the hospital, and during the next three days 147 additional cases came in, after which there was a sudden drop to an average of 4 cases a day for the week following. In view of such a mass infection, it seemed at first that the epidemic was milk borne and one of septic sore throat, and control measures were at once instituted on this basis. Pasteurization of all milk was ordered; cows and milk were examined, and nose and throat cultures taken on all food handlers and dairy workers. Several carriers of hemolytic streptococci were found among students working in the boarding halls. On the second day of the epidemic, March 13, rashes began to appear. In several cases scarlet fever antitoxin was injected intradermally at the site of the rash, and typical blanching occurred, showing the condition to be scarlet fever. Hemolytic streptococci were found in cultures made from the throats of some of the patients. In all probability all cases up to March 12, when the explosive outbreak occurred, were contact infections. The sudden appearance of 94 cases on March 12, with 80, 58, 60 and 29 the following days respectively, and then the sudden drop to 4 cases per day, strongly suggested the occurrence of a milk borne infection superimposed upon contact infection. This seemed more evident when it was learned that all of the cases which developed between March 12 and 16 had been eating at the same boarding hall. A probable clew to the source of infection was indicated upon finding several waiters in the hall to be carriers of hemolytic streptococci. Confronted then with a wide-spread outbreak of scarlet fever, the problem presented itself as to how it could be most effectively controlled. The services of Dr. Gladys H. Dick, of Chicago, were secured, who came to Berea, and gave advice and assistance in carrying out a modern, scientific program in the control of scarlet fever. It was decided not to close the school, or to discontinue classes. After due consideration of all aspects of the problem, the following general program of control was decided upon:—

1. Isolation of all cases, either in the college hospital or in dormitories set aside for that purpose.

2. Campus quarantine of all persons connected with the college, based on the results of nose and throat cultures taken on blood agar plates.

3. Skin tests (Dick Test) on all persons connected with the college to detect susceptibles to scarlet fever.

4. Active immunization of all susceptibiles with 5 graduated doses of scarlet fever toxin.

Skin tests were done, and nose and throat cultures taken on the entire population of Berea College, both procedures being carried out at the same time. Nose and throat cultures were made on 2,232 persons, 834, or 37.4 per cent of whom were positive. However, of the 834, 350 were in the

hospital with scarlet fever. Leaving this group out of consideration, there remained 1,882 on whom cultures were taken, 484 or 25.7 per cent being positive. It was known that a certain indefinite percentage of these 484 individuals had recently had mildly unrecognized cases of scarlet fever, which made it impossible to say what percentage of this group was immune carriers who had not recently had scarlet fever, and what percentage was convalescent carriers. Very few positive cultures were obtained from the nose, and all persons with positive nose cultures also had positive throat cultures. The largest percentage of positive cultures was among the student group, with the nurses coming second and the training school third. Or the 834 positive cultures which included the 350 hospital cases, 647 or 76.5 per cent were read as 4 plus, indicating that in a large majority of the individuals with positive cultures, the throat contamination was heavy. Practically all of the 350 cases of scarlet fever were in the 4 plus group. Nine and a half per cent of the positive cultures were read as 3 plus, a little over five per cent as 2 plus, and eight and nine-tenths per cent as 1 plus. Of the 834 positive cultures, 702 or 84.2 per cent were in persons with negative skin tests. However, included in the 702 are the 350 hospital cases, all of whom had negative skin tests. There were 132 persons with postive cultures who had positive skin tests. This seems rather surprising, as indicating that this number of susceptible persons had scarlet fever streptococci in their throats. According to the Dicks, however, whether a person with scarlet fever streptococci in the throat develops scarlet fever or not depends on whether or not the dosage present is sufficient to overcome the immunity present. Complete immunity may, however, result from several attacks of mild sore throat due to the presence of these organisms. As to the relation between cultures and skin tests, of the 702 with negative skin tests and positive cultures, 548, or 78 per cent, had 4 plus culture readings, but this included all of the 50 hospitals cases. Of the 132 with positive skin tests and positive cultures, 99, or 75 per cent had 4 plus culture readings, while over 11 per cent had 3 plus plates, indicating heavy contamination of the throat in a large number of susceptible persons. It was finally decided to keep all cases of scarlet fever isolated in the hospital or dormitories, and to quarantine all carriers to the college campus, release from such quarantine or isolation being based on obtaining one negative nose and throat culture. Cultures were taken once a week. In some instances, the cultures from carriers became negative in one week, the majority clearing in three weeks. In practically all carriers failing to clear in four or five weeks, pathology was found either in the nose, throat or sinuses. Among the hospitalized cases of scarlet fever, very few cultures became negative in less than four weeks, while some remained positive for five or six weeks. These findings justify the 28 day quarantine for cases of scarlet fever. Nothing in the way of treatment was found efficacious in curing the carrier condition. Fresh air and

sunshine seemed to be most helpful. After the fifth immunizing dose of toxin had been given to the susceptible group, the quarantine was raised. Of the 414 cases of scarlet fever at Berea, 139 were so mild that they were sick, clinically, for only a day or two, with temperature under 100. In 275 the temperature ranged from 100-104 for 2-5 days. A rash was recognized on 83 or a little over 20 per cent. Five others desquamated, showing rash had been present but not recognized. 56 cases were reported as having albumin in the urine. Several developed nephritis. Only 24 cases had frank emesis, although a large percentage complained of nausea. As to complications, 30 had severe cervical adenitis, 10 middle ear complications, 2 mastoiditis requiring operation, 10 peritonsillar abscess, 8 arthritis, and 7 abdominal complications, 3 requiring appendectomy. Only four of the more severe cases with complications had specific treatment, two were given scarlet fever antitoxin and two convalescent serum. All four made rapid recovery. Experience in this epidemic showed the Dick test to be a definite and reliable clinical test to determine immunity and susceptibility. While 63 cases of scarlet fever developed in persons with positive skin tests before immunization was completed, no cases occurred in persons with negative tests. Furthermore, all individuals who were convalescing from scarlet fever had negative skin tests. Of the 2,308 persons tested, 502 or 21.7 per cent were positive. The mild sore throats in this epidemic conferred immunity as well as the typical cases of scarlet fever with rash, as shown by skin tests. Active immunization of all susceptibles brought this epidemic under complete control within 7 days, or the time necessary for giving two doses of toxin. Among the 502 susceptibles only 63 developed scarlet fever subsequent to skin testing and culturing. Of these 59 developed before the second dose of toxin had been given, and the remaining four before the administration of the third dose. Of the 63, fifty-four had positive cultures at the time of skin testing. The administration of the 5 dose series of scarlet fever toxin conferred complete immunity in 97.1 per cent of the susceptible persons as indicated by a negative skin reaction to one skin test dose, with 88 per cent negative to two skin test dose, with 88 per cent negative R doses. The failure of a certain small percentage to become completely immunized after the 5 dose series of toxin is explained on the same basis as the failure of the disease itself to confer complete immunity in a small percentage of individuals, viz., a deficient immunity mechanism. Two cases immunized with the three dose series of toxin, one, two, and the other three years previously still showed complete immunity. While practically all of the persons immunized had more or less local reaction following each injection of toxin, a majority had no other disturbances. The most severe general reactions consisted of general malaise, nausea and vomiting of short duration, and various degrees of joint stiffness, all recovering with no noticeable ill after effects. The results

reported in this study of the Berea epidemic show that such an epidemic can be adequately controlled by the following means: Nose and throat cultures on blood agar plates to detect infected individuals and carriers, with isolation and quarantine, and release from same, based on the results of such cultures. Skin tests to detect susceptible individuals. Active immunization of all susceptibles with the 5 graduated doses of scarlet fever toxin recommended by the Scarlet Fever Committee. Retests, two weeks after the fifth immunizing dose, with the administration of a sixth dose to those who still react positive to the skin test. In the light of these findings it is unnecessary today for anyone to have scarlet fever. The management of this epidemic must be regarded in the light of a great confirmation and justification of the splendid work of the Dicks.

Abstracts

The So-Called Hyperglycemic Action of Insulin. By I. Neuwirth, F. Co. Tui and G. B. Wallace (Proc. Assoc. of Exper. Biol. and Med., December, 1929, p. 194).

Collens and Murlin have recently reported that the portal injection of insulin into dogs, in dosage of 0.05 to 0.1 unit per kilo weight, results in an immediate sharp rise of blood sugar of 20 to 80 mg. The rise occurs within 5 minutes and is then followed by a rapid decline. No such rise occurs following the systemic injection of the same dose of insulin. About the same time Bürger and Kramer reported that the injection of 10-20 units of insulin into the cubital vein of human beings produces a rise of blood sugar averaging 11.5%; intrajugular injection of 40 units into dogs of about 20 kilograms causes a rise averaging 28%; intraportal injection results in a rise averaging 46%. The rises occur within 5 minutes and are followed in 10-30 minutes by a rapid fall. In both of these reports the results are interpreted as showing that insulin has a glycogenolytic action of the liver and that the hyperglycemia is a physiological or normal response to this action. The present investigators carried out experiments on dogs corresponding to those described in the reports cited. They used the Lilly insulin, as did Collens and Murlin, whereas the Burroughs Wellcome product was used by Bürger and Kramer. Using small doses, they obtained no rise in blood sugar on intrajugular injection, but a rise followed intraportal injection. Their maximum rise was 15 mg. as compared to the 20-80 mg. rise of Collens and Murlin. With the larger dosage, 2-3 units per kilo (40 units total) they obtained a rise on intrajugular injection of 5 to 10%, and on intraportal injection of 15%, as compared to the 28% and 46% averages of Bürger and Kramer. Their results, however, were confirmatory of the occurrence of a rise. Repeating their experiments with crystalline insulin prepared at the Johns Hopkins laboratory, in corresponding dosages, they found the injection intrajugularly or intraportally to cause a fall of blood sugar within 1-10 minutes with no rise at 3-6 minute intervals after the injection. Since the only difference here is in the form in which the insulin is administered, it appears that the hyperglycemia when abtained, is not a true insulin action, but is due to some substance in the commercial product which acts on the liver. Fisher's experiments in which he showed that there could be obtained from the pancreas and other tissues, a toxic substance which among other actions, caused a rise in blood sugar, become of interest in this connection.

The Treatment of Lobar Pneumania with Concentrated Antipneumococcus Serum. By Russell L. Cecil and W. D. Sutliff (Jour. of A. M. A., December 29, 1928, pp. 2035).

For two years these authors carried out studies on the specific treatment of lobar pneumonia at Bellevue Hospital, largely confined to investigation of the immunologic properties and the therapeutic value of concentrated antipneumococcus serum prepared according to the method of Felton. The summary of this work appears to indicate the following: Refined antipneumococcus serum is a purified and concentrated derivative of ordinary antipneumococcus horse serum. It is usually prepared in a polyvalent form, containing immune bodies against pneumococcus types I, II and III. Its potency against type I and type II is quite high. Its potency against type III is insignificant. Concentrated serum, when injected intravenously into monkeys infected with lethal doses of pneumococcus type, promptly sterilizes the blood and

causes a rapid resolution of the pneumonic exudate. When concentrated serum is injected intravenously into patients in the early stages of pneumococcus type I pneumonia, a striking clinical effect is usually obtained. The bacteria disappear from the blood and the temperature falls to normal. Even in late cases, good results are often obtained. In type II pneumonia the clinical results are not so impressive, though here again in patients treated early, favorable results are often noted. In type III pneumonia, no clinical effect has been observed. In type IV pneumonia the beneficial effect of serum is questionable. In 441 cases of lobar pneumonia treated with refined polyvalent serum, the death rate was 30 per cent. In a control series of 444 cases the death rate was 39.2 per cent. In respect to the death rate, the refined serum produced its most striking effect in pneumococcus type I pneumonia. In a series of 153 cases of type I treated with the serum the death rate was 20.9 per cent, while a control series of 147 untreated type I cases showed a death rate of 32.6 per cent. A definite but less marked effect on the death rate was observed in cases of pneumococcus type II pneumonia treated with concentrated serum. The serum had no effect on the death rate in the pneumococcus type III pneumonia. In type IV pneumonia the death rate was lower in the treated than in the untreated series, but factors other than serum may have been responsible for this difference.

The Control of Scarlet Fever. By George F. Dick and Gladys H. Dick. (Amer. Jour. of Dis. of Children, November, 1929, p. 905).

Six years ago these investigators began the publication of a series of experiments which established a specific type of hemolytic streptococcus as the cause of scarlet fever. In these experiments it was shown that the scarlet fever streptococcus produces a potent soluble toxin which is responsible for the toxemia, nausea and rash, and that recovery from the disease with subsequent immunity depends on the production of an antitoxin. The conclusions as to the etiology, specific toxin and antitoxin of scarlet fever have been verified by numerous reports in this and other countries, particularly that done by Nicolle in the Pasteur Institute in Tunis, where all the crucial experiments were repeated, including even the production of experimental scarlet fever in human beings. Results are now available from observations made during the last six years on a series of 32,440 persons on whom skin tests were made, on 11,584 susceptible persons who were immunized against scarlet fever by the injection of graduated doses of the sterile toxin, and on groups of susceptible persons found to be infected after exposure who were given prophylactic doses of the antitoxin. All these persons were exposed to scarlet fever in one or more epidemics. Results are also available from observations in a series of 967 cases of scarlet fever in which the antitoxin was employed therapeutically. The reliability of the skin test in determining susceptibility to scarlet fever is shown by the results in 20,856 persons with spontaneously negative reactions. All of these immune persons passed through one epidemic of scarlet fever, and some went through several epidemics without contracting the disease, with the possible exception of one boy who showed a desquamation of the feet and gave a history of sore throat. The most severe test of the skin reaction was found in a group of 2,157 pupil nurses and interns who were allowed to go duty in contagious disease services when their skin tests were found to be spontaneously negative. In spite of prolonged and intimate exposure to scarlet fever, none of this group contracted the disease. Regarding the incidence of immunity to scarlet fever after early infancy this depends on conditions that favor exposure to the disease. Thus in an overcrowded institution the incidence of susceptibility may be as low as 10 per cent, while in rural or suburban groups it may be as high as 85 per cent. In a series of skin tests, it will be found that the positive reactions show all gradations from small areas of faint color to intensely red reactions 3 to 5 cm. in diameter. These differences in the intensity of the skin reactions correspond to differences in

degree of susceptibility, and partly explain the great variation in severity of scarlet fever. The intermediate stages of the reaction also indicate that in many persons immunity to scarlet fever is acquired gradually through repeated infections with the streptococci of scarlet fever without the development of a typical attack of the disease. It has been learned that one attack of scarlet fever sore throat does not necessarily confer complete immunity, but typical attacks of scarlet fever usually result in complete immunity, as indicated by negative skin reactions in patients convalescent from scarlet fever and by the comparative infrequency of second attacks. Active immunization with graduated doses of sterile scarlet fever in 12,785 susceptible persons caused no injury in any instance. In three institutions urine analyses were made before, during and after immunization, and there was no evidence of nephritis caused by the immunization. Some persons who had nephritis were immunized without causing an exacerbation of the condition. In a large series, including highly susceptible persons, general reactions may be expected after each dose in about 10 per cent. The most highly susceptible persons usually react more strongly on the first doses; others may not have any reactions until the fourth or fifth dose is given. As a rule, reactions after the last and largest dose are fewer and milder than after the smaller first doses. The immunizing doses should be accurately graduated, and it is important to give them in the proper sequence in order to avoid unnecessarily severe reactions. Experimentally, as much as 20 cc. of undiluted toxin containing nearly 1,000,000 skin test doses have been injected without causing injury and without producing nephritis in human beings. Strong warning is given against the use of the Larson ricin treated toxin; in spite of repeated warnings it has been widely distributed and employed by physician in unsuccessful attempt to control epidemics of scarlet fever. The doses of sterile toxin for active immunization should be graduated, beginning with 500 skin test doses in the first injection and increasing to 80,000 or 100,000 skin test doses in the last. The injections are made subcutaneously at intervals of one week. If the full amount is given in each dose, the five doses may be counted on to immunize completely 95 per cent of susceptible persons, and to modify considerably the susceptibility of the rest. Two weeks after the last dose is given another skin test is made, using 0.1 cc. of the skin test solution or one skin test dose on the right arm, and 0.2 cc., or two skin test doses on the left arm. If the reaction on either arm is positive, the fifth dose is repeated. Unless the immunization is carried to the point of a negative skin reaction, complete protection against scarlet fever cannot be expected, although the severity of a subsequent attack would be modified by the partial immunization. The duration of active immunity, as well as the degree of immunity, depends on the amount of toxin injected. Retests made at intervals of 1, 2 and 3 years indicate that more than 90 per cent of these immunized to the point of an entirely negative skin reaction retain their immunity. Between 5 and 9 per cent slip back and require a second immunization. By means of nose and throat cultures on blood agar plates, skin tests for susceptibility, active immunization of susceptible persons with the toxin and the use of antitoxin prophyactically in infected susceptibles, it is possible, in a group small enough to test and culture in one day, to bring an epidemic of scarlet fever under control in forty-eight hours. The passive protection conferred by a prophylactic dose of any antitoxin is transient, lasting at the most from two to three weeks. Active immunization with the toxin should be begun in the infected susceptibles one week after the prophylactic dose of antitoxin is given. Scarlet fever antitoxin may be employed therapeutically with advantage in all cases of scarlet fever as soon as the appearance of the rash suggests the diagnosis. Given early, in adequate dosage, scarlet fever antitoxin gives brilliant results. The patient sometimes recovers so quickly that the attending physician wonders whether or not he could have been mistaken in his diagnosis of scarlet fever.

The longer the patient goes without antitoxin, the less he benefits from it when given. It should not be withheld until it becomes apparent that the attack is a severe one, but should be given in time to prevent the devolopment of a severe attack. Reports as to the effect of scarlet fever antitoxin in reducing the complications are sometimes conflicting, due to delay in administering the serum in some cases, or to the use of poor preparations of antitoxin. Most scarlet fever antitoxins of European manufacture are considerably weaker than the best American serum. Samples of antitoxin purchased in Europe have been found to contain from a trace to 5,000 neutralizing units per cubic centimeter, while the best supplied in America contains 30,000 units. Even with the delay involved in the diagnosis of scarlet fever in hospital cases, it has been shown that scarlet fever antitoxin reduces the incidence and severity of complications. Results in the antitoxin series, which included the more severe cases, compared with the results in the control series, comprised of the cases which, on admission to the hospitals, appeared to be less severe, show that mastoiditis occurred three times as frequently in the control series as in the antitoxin series; that post scarlatinal nephritis appeared four times as frequently in the control series as in the antitoxin series, and that in spite of the milder appearance of the disease at the onset, the death rate in the control series was twice that in the antitoxin series.

Bacteriology of the Blood and Joints in Rheumatic Fever. By Russell L. Cecil, Edith E. Nicholls and Wendell J. Stainsby (Jour. of Exper. Med., November, 1929, p. 617).

During the Spring of 1928, 29 patients with acute rheumatic fever were subjected to blood cultures, of whom 9, or 31 per cent, yielded a streptococcus. The higher percentage of positive cultures in the 1929 series appears to have been due to improved cultural methods. Of the 35 strains of streptococci recovered from blood cultures, 33 have been classified as alpha streptococci (Str. viridans); one as a beta streptococcus (Str. hemolyticus); and a gamma streptococcus (Str. anhemolyticus). Some of the viridans strains produced very little green on blood media. Agglutination and absorption tests indicate that the strains of streptococcus viridans recovered from the blood of patients with rheumatic fever show a tendency to fall into specific biological groups. In 7 patients with rheumatic fever who were subjected to cultures from affected joints, 5, or 71.4 per cent, yielded a streptococcus viridans. In 3 patients in whom green streptococci were recovered from both the blood and joint, agglutination and absorption tests proved the identity of the strains isolated from the two sources. These findings corroborate those of previous investigators and make it difficult to escape the conclusion that rheumatic fever is a streptococcal infection usually of the *alpha* or *viridans* type. The pathogenesis of rheumatic fever in respect to the joint lesions appears to be analogous to that of infectious arthritis and gonococcal arthritis. Bacterial allergy probably influences the clinical picture in all three conditions, but in each instance the joint manifestations are primarily dependent upon localization of bacteria in the joint, with subsequent infection.

Reviews

Bacteriology for Nurses. By HARRY W. CARRY, A.B., M.D., Assistant Bacteriologist, Bender Hygienic Laboratory, Albany, N. Y.; Pathologist to the Samaritan Hospital, Trop, N. Y., Cohoes Hospital, Cohoes, N. Y., and Putnam Memorial Hospital, Bennington, Vermont. Third Revised and Enlarged Edition. Illustrated with 43 engravings and 1 colored plate, 282 pages, F. A. Davis Company, Philadelphia, 930. Price in cloth, $2.25.

The second edition of this book appeared ten years ago, and since that time much advance has been made in bacteriology. In order to incorporate this new work, it has been necessary to rewrite the entire book and to enlarge it. Many of the subjects have been discussed in more detail than might seem to be required in a text-book for nurses, but the requirements of the National League for Nursing and the State Board of Education are more exacting than they were formerly. The author has had it in mind to prepare a book to serve the nurse, not only as a text-book, but for reference as well. This book appears to cover the ground of general bacteriology sufficiently thoroughly for the purpose for which it is intended. A series of fifteen laboratory exercises is given, and these afford practical application of the material given in the text. The book is written in clear and simple language, and the exposition is also clearly stated. It may be recommended for the purpose for which it was written, a text-book of bacteriology for the practical nurse.

Surgical and Medical Gynecologic Technic. By THOMAS H. CHERRY, M.D., F.A.C.S., Professor of Gynecology in the New York Post-Graduate Medical School and Hospital, etc. 678 pages, 558 half-tone and line engravings, from photographs and pen and ink drawings by the author. F. A. Davis Company, Philadelphia, 1929. Price in cloth, $8.00.

This book was written with the object of presenting to the medical profession a technical work on gynecology. His experience as a teacher for the past fifteen years in the New York Post-Graduate Medical School has impressed him with the needs of graduate medical students in both surgical and non-surgical procedures. The book is not intended as a textbook for the undergraduate student of medicine, as the necessary rudiments, such as physiology, symptomatology and diagnosis have largely been omitted. To the practitioner of medicine, who is constantly coming in contact with gynecological patients and to whom they look for relief, this book is intended to aid him in applying appropriate modern methods of diagnosis and therapy. To the practitioner who has had and comprehends surgical technic, with especial leaning towards gynecology this book is further intended to help him to select standard operative procedures for those patients requiring surgical intervention. The description of operations is confined to one standard method, which in his own experience has given the best result. The author has attempted to represent in this work a single method of therapy, based upon anatomy and pathology and to give sufficient illustrations to make this logical and comprehensive. The illustrations, while homemade, serve their purpose very well, and are on the whole very good. The arrangement of the material is very good, and the various technical methods are clearly presented.

Incompatibility in Prescriptions and How to Avoid It. To Which is Added a Dictionary of Incompatibilities. By THOMAS STEPHENSON, D.Sc., Ph.C., F.R.S.Edin.,

F.C.S., Editor of the Prescriber; Some Time Examiner to the Pharmaceutical Society of Great Britain; Author of the Prescriber's Pharmacopoeia. New Edition, Revised and Enlarged. 61 pages. Paul B. Hoeber, Inc., New York, 1929. Price in cloth, $1.50.

This little book originally appeared in 1915 in the form of a 32-page pamphlet. It apparently filled a want, as reprintings were called for in 1916 and again in 1921. A second edition carefully revised was issued in 1924, and reprinted in 1925. As only a few copies of this remain unsold, this new edition has been called for. Opportunity has been taken for a thorough revision of the entire work, and of adding for reference purposes a complete Dictionary of Incompatibilities. It is now possible to ascertain with a minimum of trouble the exact difficulties to be encountered in dispensing any of the drugs now in common use. The work is practically a new book, and its size has been increased to double that of the original pamphlet. As far as possible the incompatibilities described in the following pages have been verified experimentally. It is intended in these pages to study the subject of incompatibility in a systematic manner, illustrating with examples the various difficulties most likely to be met with by the physician in ordinary practice. For the latter this little volume will prove to be most serviceable and practical.

Outline of Preventive Medicine. For Medical Practitioners and Students. Prepared Under the Auspices of The Committee on Public Health Relations of the New York Academy of Medicine. 21 Contributors. Editorial Committee: Frederic E. Sandern, Charles Gordon Heyd and E. H. L. Corwin. 389 pages. Paul B. Hoeber, Inc., New York, 1929. Price in cloth, $5.00.

Repeated requests for an outline of the practical features in the prevention of disease induced the Public Health Relations Committee of the New York Academy of Medicine to appoint a sub-committee for the purpose of assembling and supervising the publication of a brief manual of the subject. Each contributor to this volume has written of the ways in which his specialty is related to preventive medicine, limiting his contribution to salient suggestions based on individual experience, without any attempt at textbook completeness. The list of contributors comprises Harlow Brooks, Robert A. Cooke, E. H. L. Corwin, Charles L. Dana, R. L. Dickinson, A. B. Duel, H. S. Dunning, Alice Hamilton, C. G. Heyd, R. A. Hibbs, Arnold Knapp, S. W. Lambert, G. M. MacKee, J. A. Miller, James Pedersen, Bernard Sachs, F. E. Sandern, J. B. Squier, P. Van Ingen, B. P. Watson and C. H. Watson. The various contributions making up this volume constitute a valuable resumé of the practical features in disease prevention, and should be of great value to the general practitioner in preparing himself for the part he should play in furthering the cause of preventive medicine. Much valuable information is contained herein, and the volume is not so technical that it cannot be recommended for use by laymen.

Synopsis of the Practice of Preventive Medicine. As Applied in the Basic Sciences and Clinical Instruction at the Harvard Medical School. Edited by Dr. SHIELDS WARREN. 194 pages. Harvard University Press, Cambridge, 1929.

This book has a similar aim, and covers practically the same ground as the Outline of Preventive Medicine prepared by the New York Academy of Medicine. It was not conceived as a text or reference book but merely as a depository for such points as seemed of possible value in emphasizing the importance of preventive medicine for the practitioner. The various chapters represent the composite ideas of many of the faculty, and stress those prophylactic measures that should help the doctor in protecting the health of his patients. The collection represents each department of the school in a presentation of the pertinent things relating to prevention that each department felt could and should be taught in that department. As a matter of fact it provides essentially a small, collective text-

book of general practice of preventive medicine, and is intended to further the permeation of the whole curriculum with the atmosphere of preventive medicine as equal in strength to that of curative medicine. In carrying this out, purely preventive measures have been blended with those that check or control the progress of slight or early chronic diseases. There is a very great unevenness in the various sections; those on Bacteriology, Medicine, Surgery and Pediatrics contain the most pertinent material. The two pages devoted to syphilology represent a good opportunity lost. As compared with that produced by the New York Academy of Medicine, the Harvard book has much less material and in general is less specific in its application to preventive medicine and less practical.

Pettibone's Textbook of Physiological Chemistry. With Experiments. Revised and rewritten by J. F. McCLENDON, Ph.D., Professor of Physiological Chemistry, Medical School, University of Minnesota. Fourth Edition. 368 pages, 17 illustrations. The C. V. Mosby Company, St. Louis, 1929. Price in cloth, $3.75.

The author's aim in writing this book was to prepare an intermediate textbook which would cover the general field of physiological chemistry in such a way as to give students a familiarity with compounds important from a biochemical viewpoint and to acquaint them with the fundamental processes which go on in the animal body. He has attempted to avoid confusing the beginner with lengthy discussions of debated points, but to set forth as clearly as possible the present status of our knowledge. The material is so chosen that the book may be used for intermediate classes, or for advanced work when supplemented by lectures. The appended laboratory work has been drawn from the manual in use in his classes during the last five years. Since this first edition the following ones have preserved the original character of the work, with much new material added, both in the text and laboratory section, and some of the older methods have been omitted. This fourth edition has been revised and rewritten, so that it has been brought up to date, and now serves as a complete textbook of physiological chemistry. The material is presented in a clear and logical manner, and with a readable style.

An Outline of Endocrinology. By W. M. CROFTON, B.A., M.D., Lecturer on Special Pathology, University College, Dublin; Pathologist, Dr. Steevens Hospital, Dublin. Second Edition. 163 pages, 53 figures. William Wood & Co., New York, 1929. Price in cloth, $3.00.

This book consists of the substance of lectures given annually by the author since 1910. He has had in mind the production of a short but sufficiently comprehensive textbook on the Internal Secretions, both for the medical student and the general practitioner. The reception of the first edition was so encouraging that the author has brought out this second edition, brought as far as possible up to date with the very rapidly advancing work on the endocrine mechanisms. The chapters include those on the pineal gland, pituitary gland, suprarenals, thyroid, parathyroids, thymus, gonads, gastrointestinal hormones, pancreas and liver, with epilogue, and supplementary notes on recent advances. The main points of our knowledge of endocrinology are given, somewhat superficially in some instances. Microbic infection as the cause of the fundamental derangements of the endocrine glands is too much emphasized, and the author appears somewhat over-enthusiastic also in his statements as to the successful use of glandular therapeutic preparations.

The Eye in General Medicine. The Constitutional Factor in the Causation of Disease. With Special Reference to the Treatment of Diseases of the Eye. By A. MAITLAND RAMSAY, M.D., LL.S., Fellow of Royal Faculty Physicians and Surgeons, Glasgow; Consulting Ophthalmic Surgeon, Glasgow Royal Infirmary. Second Edition of "Diathesis and Ocular Diseases." 255 pages. Wil-

liam Wood & Co., New York, 1929. Price in cloth, $5.00.

This little book was originally entitled "Diathesis and Ocular Diseases," when first published in 1909, and has been out of print for some years. This, the second edition, has been almost wholly rewritten, and so completely rearranged that, although the theme is the same, the book itself is new. It claims to be no more than a personal record of a fairly long clinical experience, and is published in the hope that it may be useful both in the junior practitioner and to the young ophthalmologist. Although the book is intended to be read as a whole, yet each chapter is complete in itself. This book contains a good deal of very important information with reference to some of the ocular manifestations of disordered carbohydrate metabolism, defective elimination, etiology of acute primary glaucoma, medical aspects of eye strain, pneumonococcal ulceration of cornea, toxic inflammation of the iris, ocular manifestations in cardiovascular disease, etc., of which the general practitioner should have knowledge. For him this book should possess a special practical value.

The Newer Knowledge of Nutrition. By E. V. McCollum, Ph.D., Sc.D., Professor of Chemical Hygiene in the School of Hygiene and Public Health, of the Johns Hopkins University; and Nina Simmonds, Sc.D. (Hygiene), Formerly Associate Professor of Chemical Hygiene in the School of Hygiene and Public Health, of the Johns Hopkins University. 594 pages, 34 illustrations. Fourth Edition. Rewritten. The MacMillan Company, New York, 1929. Price in cloth, $5.00.

Advances along several lines since the publication in 1925 of the third edition of this book make necessary an extensive revision in order to include the most important studies relating to several phases of nutrition. The general plan of the third edition has been preserved, and while much of the former edition has been retained, the book has been essentially rewritten for the purpose of elimination of some parts and the condensation of others, so as to make room for the new experimental work without enlargement of the volume. The original purpose of preparing a comprehensive treatise on the science of nutrition, in which the newer knowledge is presented in its historical setting, has been adhered to. The literature has been examined to May, 1929. The biblography of the third edition contained 1870 references. To cover the entire field of nutrition with the same thoroughness today would require the citation of about 8000 communications. Obviously it was not possible to include a complete bibliography without making the volume too unwieldly. Furthermore, the bibliography of nutrition is so easily available in Chemical Abstracts and in the Quarterly Cumulative Index Medicus, which are accessible in numerous libraries that it would hardly be justified in publishing an exhaustive list of publications on the subject. For these reasons the authors have included only a select bibliography, but have made an effort to include all papers which contain important special lists of literary citations. Among the most striking features of the new edition are the recent discoveries concerning the etiology and and treatment of the anemias, both secondary and pernicious; discussion of all that is known about the dietary requirements of blood regeneration; the experience of recent years in the control of goiter through the provision of iodine; recent researches on the relation of diet to bone development, the calcification of fractures, and the prevention of rickets. The story of the discovery of ergosterol, the mother substance of vitamin D, the active principle of cod-liver oil is given. The physiologic effects of light and the changes it effects in ergosterol, the present status of light therapy through the use of sunlight and the various sources of the ultraviolet rays, and the nutritional influence of the infrared rays are discussed in full; as is also the relation of diet to pellagra. The chapter on the dietary habits of man is of especial interest. All is told in an agreeable easy style; and the material assembled in this work makes it of first class importance to the physician.

College News Notes

Announcement has been made recently of the retirement of George E. Vincent, Ph.D., from the Presidency of the Rockefeller Foundation. Dr. Vincent was the guest speaker at the annual Banquet of the College at Boston last year. He is succeeded by Dr. Max Mason.

Dr. James H. Hutton (Associate), President-Elect of the Chicago Medical Association, addressed the Franklin County Medical Society at Eldorado, November 26, on "Endocrine Disturbances and the Common Cold."

Dr. Albert M. Snell (Fellow), Rochester, Minn., addressed the Northern Minnesota Medical Association at its last annual meeting, on "Recent Advances in Endocrinology."

Dr. W. W. Duke (Fellow), Kansas City, spoke before the St. Louis Medical Society, December 10, on "Allergy as Related to the General Practice of Medicine."

Dr. Frederick Epplen (Fellow), Seattle, spoke on internal medicine and diagnosis during the opening exercises of the new medical library of the Spokane County Medical Society during November.

Dr. Julius H. Hess (Fellow), Chicago, gave an exhibition before the U. S. Live Stock Sanitary Association, December 4-6, at Chicago on "Clinical Aspects of Human and Animal Rabies," illustrated by moving pictures.

Dr. Carl V. Weller (Fellow), Ann Arbor, Mich., was made Secretary of the American Society for Experimental Pathology at its last annual meeting.

Dr. Kenneth M. Lynch (Fellow), Professor of Pathology at the Medical College of South Carolina, was elected President of the American Society of Tropical Medicine at its last annual meeting.

Dr. G. Morris Golden (Fellow), Professor and Head of the Department of Medicine, Hahnemann Medical College and Hospital of Philadelphia, was the chief speaker at the December meeting of the Germantown Homeopathic Medical Society in Philadelphia held on December 16. His topic with a blackboard presentation in colors of "Methods Useful to the Practitioner in Estimating the Cardiac Function."

Dr. Vernon C. Rowland (Fellow), Cleveland, Ohio, was elected President of the Academy of Medicine of Cleveland at the annual meeting o fthe Board of Directors recently. Dr. Rowland is Visiting Physician at St. Luke's Hospital, Associate Professor of Medicine in the Western Reserve University Dental College and Editor of the Academy Bulletin.

Dr. H. V. Paryzek (Fellow), Cleveland, Ohio, was elected Vice President of the Academy at the same meeting. Dr. Paryzek has been a Director of the Academy for several terms. He is Instructor in Medicine at Western Reserve University School of Medicine, Visiting Physician to the Cleveland City and St. Alexis' Hospitals and Director of Laboratories at St. Alexis' Hospital.

Dr. E. Roland Snader, Jr. (Fellow), Philadelphia, is author of "A Report of two Cases of Thyroid Obesity," which appeared in the November Issue of The Hahnemannian Monthly.

Dr. James L. McCartney (Fellow), Hartford, Conn., delivered a radio address entitled "Why Folks Fail" over Station WTIC, Hartford, Conn., on December 26.

Dr. Henry I. Klopp (Fellow), Superintendent of the Allentown, Pa., State Hospital, read the Seventeenth Annual Report of that institution at the meeting of the Homeopathic Medical Society of the State of Pennsylvania held at Philadelphia in September. This very interesting report was published in the November edition of the Hahnemannian Monthly.

Dr. Bernard L. Wyatt (Fellow), Tucson, Ariz., has accepted an invitation to do the editorial work from the medico-social point of view on Acta Rheumatologica. At the Budapest Congress of the Ligue Internationale Contre Le Rheumatisme, it was decided to publish Acta Rheumatologica, the editorial staff to be recruited from all affiliated nations. The invitation was extended to Dr. Wyatt through Dr. J. Van Bremmen, Chief Editor and Director of the Acta Rheumatologica, Amsterdam, Holland.

Dr. Sinclair Luton (Fellow), St. Louis, Missouri, addressed the Fayette and Clinton (Illinois) County Medical Societies at Greenville, Illinois, recently on "Common Disorders of the Heart."

At the 28th annual meeting of the Frisco System Medical Association at Tulsa, Okla., during October, Dr. Luton presented "Moving Pictures of the Heart Action."

At the annual meeting of the Southern Illinois Medical Association at Benton, Ill., November 7-8, 1929, Dr. Luton presented the following papers:

"Endocarditis and Valvular Disease," illustrated with slides; "Valves of the Heart in Action," illustrated by motion pictures.

Dr. Carl V. Vischer (Fellow), Philadelphia, and his son, Carl V. Vischer, 3rd, ten, took part in the Cornerstone laying of the new $1,500,000 St. Luke's Childrens' Homeopathic Hospital on December 11. Dr. Vischer is a Visiting Physician of the institution and is the son of the Founder and first Suregon in Chief of St. Luke's Hospital.

Dr. Francis M. Pottenger (Fellow), Monrovia, Calif., has become a Life Member of the American College of Physicians, as of January 1, 1930. This is a manner in which many Fellows of the College could contribute to the cause of Internal Medicine, for by building up a fair Endowment Fund for the College, its work can be expanded to greater fields.

Dr. Kano Ikeda (Fellow), St. Paul, Minn., has accepted the directorship of the laboratories of the Charles T. Miller Hospital, St. Paul, beginning January 1, 1930. Dr. Ikeda was formerly Director of Laboratories at the St. Luke's and Children's Hospitals, St. Paul.

At the 46th annual convention of the Tri-States Medical Association of Mississippi, Arkansas and Tennessee, at Memphis, January 14-16, 1930, Dr. George R. Minot (Fellow), Boston, Dr. W. McKim Marriott (Fellow), St. Louis, Dr. Charles C. Bass (Fellow), New Orleans and Dr. Henry A. Christian (Fellow), Boston, were among the guest speakers.

Dr. Russell S. Boles (Fellow), Philadelphia, was recently appointed Visiting Physician to the Philadelphia General Hospital.

Armistice Night was celebrated by the Philadelphia County Medical Society at a dinner at which Surgeon Generals M. W. Ireland (Fellow), Charles E. Riggs (Fellow) and Hugh S. Cumming (Fellow) of the U. S. Army, Navy and Public Health Service, respectively, were speakers.

Dr. John A. Lepak (Fellow), St. Paul, Minn., has become a Life Member of the American College of Physicians, as of January 1, 1930.

Dr. W. H. Stoner (Fellow), formerly with E. R. Squibb & Sons, has recently become affiliated with Hoffman-La Roche, Inc., of Nutley, New Jersey.

The College acknowledges receipt of the following publications by Fellows of the College:

"The IIndividual's Responsibility and The State's Responsibility," by Dr. Frederic J. Farnell, Providence, R. II.

"Mouth Infection," by Dr. Oliver T. Osborne, New Haven, Conn.

The publications of members are sought by the College, in order that it may have a more or less complete library of work produced by its members.

Dr. S. Calvin Smith (Fellow), Philadelphia, has delivered the following addresses recently:

"Heart Irregularities" before the Montgomery County Medical Society, Norristown, Pa., November 6;

"The Clinical Significance of the Irregular Pulse," before the Clearfield County Medical Society, Clearfield, Pa., November 22;

"The Heart in Advancing Years," before the Harrisburg Academy of Medicine, Harrisburg, Pa., on December 22.

Dr. Daniel N. Silverman, (Fellow), was elected President of the New Orleans Gastro-Enterological Society at its annual meeting January 23, 1930.

Dr. John H. Musser, (Fellow), was the orator of the evening and spoke on "Gastric Ulcer."

Dr. Ernest H. Falconer, (Fellow), San Francisco, Calif., has subscribed to the Endowment Fund of the College and becomes a Life Member, as provided in the By-Laws.

Dr. Benjamin Goldberg, (Fellow), Chicago, will give the Annual Address at the meeting of the Boston Tuberculosis Association on the afternoon of Monday, February 3, 1930. His subject will be "Present Needs in Tuberculosis Control." In the evening Dr. Goldberg will address the Trudeau Society of Boston on "The Medical Aspects of Phrenic Surgery."

Dr. Konrad Birkhang, (Fellow), gave the annual Sigma Nu address at Mount Union College, Alliance, Ohio, on January 16th, on "An Epic in Experimental Medicine: The Life of Dr. Otto Obermeier." On January 15th, he addressed the Alliance Medical Society, Alliance, Ohio, on "Bacterial Allergy in Rheumatic Fever, Tuberculosis and Syphilis."

Dr. J. Dwight Davis, (Fellow), formerly of the Mayo Clinic at Rochester, Minnesota, has opened offices at 802 Wilshire Medical Building, 1930 Wilshire Boulevard, Los Angeles, Calif.

The Committee on Organization of the First InIternational Congress on Mental Hygiene, acting as representatives of national mental hygiene societies and related organizations throughout the world, has announced a world meeting on medical hygiene to be held at Washington, D. C., May 5-10, 1930. The Committee on Organization has asked the co-operation of all Governments, voluntary organizations and individuals interested in better mental health for all people, in making this first world Congress on Mental Hygiene of vital significance to the cause it would serve.

Dr. William A. White, (Fellow), Washington, D. C., is President of the Congress; Dr. Hugh S. Cumming, (Fellow), Surgeon-General of the U. S. Public Health Service, is a vice president; Dr. Charles F. Martin (Master), Montreal, is an honorary vice president.

The Elliott Chair of Preventive Medicine and Public Health has recently been established at Queen's University at Kingston, Ont., by Mr. Samuel Insull, of Chicago, in honor of Dr. Arthur R. Elliott, (Fellow), Chicago. Dr. Elliott is a Queen's graduate. Dr. John Wyllie, M.A., M.B., Ch.B., BS., D.P.H., was appointed to this Chair on December 12.

Dr. Walter W. Palmer, (Fellow), New York, was one of the speakers at the opening of the new $2,000,000 New York State Psychiatric Institute and Hospital, a unit of the Medical Center at Broadway and 168th Street, on December 3.

Dr. Ray M. Balyeat, (Fellow), Oklahoma City, during November, addressed the York-

ville County Medical Society, New York, on "Importance of Pollen as an Etiologic Factor in Allergic Diseases in the Southwest Compared with Other Sections of the United States."

Dr. Lawrence Litchfield, (Fellow), Pittsburgh, was the recipient of a testimonial dinner in December, just previous to his departure south for the winter. Dr. William S. Thayer, (Fellow), Baltimore, was one of the speakers.

Dr. Alexander B. Moore, (Fellow), Rochester, Minn., and Dr. John T. Murphy, (Fellow), Toledo, were elected President-Elect and Secretary, respectively, of the American Roentgen Ray Society at its annual meeting in Toledo, December 6.

Dr. Henry A. Christian, (Fellow), Boston, delivered the annual lecture at the Scripps Metabolic Clinic at La Jolla, Calif., January 25, on "Chronic Nonvalvular Heart Disease: Its Causes, Diagnosis and Management."

Dr. Charles A. McKendree, (Fellow), New York, has been appointed Assistant Professor of Clinical Neurology in the College of Physicians and Surgeons of Columbia University.

Dr. Aldred Scott Warthin, (Master), delivered the De Lamar Lecture on "The Incidence of Latent Syphilis in the Population," at the School of Hygiene, Johns Hopkins University Medical School, on Tuesday, January 21, 1930.

Dr. William D. Sansum, (Fellow), Santa Barbara, Calif., has become a Life Member of the American College of Physicians, as of January 1, 1930, by subscription of the Life Membership Fee to the College Endowment Fund.

Dr. Wilfred M. Barton, (Fellow), Washington, D. C., appeared on the program of physicians presenting a series of clinics at the University of Maryland, Division of Medical Extension, Baltimore, Maryland, on Thursday afternoons during January and February of 1930.

Dr. Henry J. John, (Fellow), Cleveland, Ohio, is the author of an article, entitled "Problems in Diabetes," printed in the Journal of the Oklahoma State Medical Association, January, 1930.

Dr. Edgar V. Allen, (Associate), Rochester, Minn., has been in Europe since April of 1929 pursuing undergraduate work. He studied two months at the Medizinische Universitäts Klinik at Leipsig under the supervision of Professor Morawitz, Director of the Klinik. During Dr. Allen's work at the Klinik, he received an appointment as Fellow of the National Research Council.

From Leipsig, he visited, with Dr. C. H. Mayo, the medical clinics in Berlin, and then went to Zurich, Switzerland, for three weeks' visit to the clinics there. In August, 1929, he went to Munich, where he has been working with Geheimrat Professor Friedrick von Müller in Medicine and with Geheimrat Professor Borst in Pathology. More recently, Dr. Allen has been working in Forschung Anstalt für Psychiatrie. He has also visited the clinics of Paris, Prague and Vienna. He plans to go to London to study with Sir Thomas Lewis during the months of May, June and July of 1930, and return to America during August.

The following gifts of publications by members of the College are acknowledged:

Dr. Curran Pope, (Associate), Louisville, Ky., Book, "Practical Hydrotherapy."

Dr. Miles J. Breuer, (Fellow), Lincoln, Nebr., Reprint, "The Present-Day Conception of Tuberculosis."

Dr. Ralph O. Clock, (Fellow), Pearl River, N.Y., Reprints: "The Use of Normal Horse Serum for the Treatment of Burns." "Hay-Fever and its Treatment with Clycerolated Pollen Antigen."

Dr. Oliver T. Osborne, (Fellow), New Haven, Conn., Reprint, "Mouth Infection."

Dr. Walter M. Simpson, (Fellow), Dayton, Ohio, Reprints:

"Primary Chondroma of the Lung."

"Tularemia (Francis's Disease)

"Tularaemia (Francis' Disease)"
"Tularemia—Study of Rapidly Fatal Case".
"Tularemia (Francis' Disease)—A Clinical and Pathological Study of Forty-Eight Non-Fatal Cases and One Rapidly Fatal Case, with Autopsy, Occurring in Dayton, Ohio."
"A Clinical and Pathological Study of Fifty-five Malignant Neoplasms of the Thyroid Gland."
"Tumor-Thrombosis of the Inferior Vena Cava with Four Additional Cases of Neoplastic Invasion."
"Aberrant Pancreatic Tissue—An Analysis of 150 Human Cases with a Report of a New Case."
"Tularemia (Francis' Disease)—Report of Four Additional Cases."
"Three Cases of Thyroid Metastasis to Bones."
"Graves' Constitution (Warthin."
"Diffuse Vertebral Metastasis of Prostatic Carcinoma Without Bony Changes."
"Actinomycosis of the Vertebrae (Actinomycotic Pott's Disease)."
"Tularemia (Francis' Disease): A Clinical and Pathological Study of Sixty-one Human Cases Occurring in Dayton, Ohio."
"Tularemia (Francis' Disease): Experiences with Fifty-three Cases Occurring in Dayton, Ohio."
"The Surgical Pathology of Graves' Disease; With Special Reference to Its Prognostic Significance."

Dr. Carl V. Vischer, (Fellow), Philadelphia, Pa., Reprints:

"Acute Miliary Tuberculosis: Report of Cases with Recovery."
"Report of Arthritis Conference, Hahnemann Hospital."

Dr. William C. Voorsanger, (Fellow), San Francisco, Calif., Reprint, "Vaccine Therapy in Infectious Bronchitis and Asthma."

Dr. Coursen B. Conklin, (Fellow), Washington, D. C., Reprints:

"Diagnostic Problems Peculiar to Pediatrics, with Special Reference to Child-Parent Psychology."
"Infant Feeding."
"Congenital Atresia of Bile Ducts."
"Aspiration of Stearate of Zinc Powder in Infancy."
"Acute Primary Pneumonia."
"Some Observations on the Correlation of Physical Findings in the Chest in Infancy with Pathology."

Dr. Frederick J. Farnell, (Fellow), R. I., Reprint, "The Individual's Responsibility and The State's Responsibility."

Dr. Lorenz W. Frank, (Fellow), Denver, Colo., Reprints:

"Tuberculosis and Goitre."
"The Basal Metabolism in Pulmonary Tuberculosis."
"Rheumatic Fever."

Dr. Philip B. Matz, (Fellow), Washington, D. C., Reprint, "The Surgical Treatment of Pulmonary Tuberculosis in the United States Veterans' Bureau."

Dr. John A. Murphy, (Associate), Philadelphia, Pa., Reprint, "Pollen Suspensions: A Preliminary Report."

PLACEMENT SERVICE

The Executive Offices have on file a few physicians who are seeking new appointments. Some of these are Associates or Fellows of the College. There are at present one well qualified Internist and one Radiologist, who are seeking new connections with Fellows of the College who desire assistants.

The Executive Offices serve as a sort of clearing house through which members of the College may seek assistants, or may seek new connections. The College will assist in securing authentic information, but cannot assume responsibility in connection with recommendations. The purpose of the Executive Offices is to serve the membership in the best possible way. Inquiries are invited.

Attention of members of the American College of Physicians is called to the following Fellow who is desirous of making new connections. Correspondence should be addressed to the Executive Secretary, E. R. Loveland, 133-135 S. 36th Street, Phila-

delphia, Pa., mentioning the number preceding the following announcement:

No. 1—Internist, M.D., F.A.C.P., 38 years of age, married, ten years private practice, desires association with older man or clinic where there are opportunities for advancement. Mainly interested in diseases of chest and stomach. Will go anywhere but prefer city in South West. Personal interview may be arranged.

OBITUARY

Dr. Harry Monroe McClanahan, (Fellow), Omaha, Nebr., died November 20, 1929; aged 73

Dr. McClanahan, a Pediatrist, received his early education at Monmouth, Illinois, and later took his A.B. Degree in 1875. He attended the Jefferson Medical College of Philadelphia, graduating with the degree of Doctor of Medicine in 1878. He was resident physician at Jefferson Hospital, Philadelphia, 1878-79; practiced at Alexis, 1879-80; was agency physician at Ft. Belknap, Montana, 1880-81; practiced at Woodhull, Illinois, 1881-89; and went to Omaha, Nebraska, in 1889. He had been Professor of Pediatrics at the Omaha Medical College (now the University of Nebraska College of Medicine) since 1892, being made Professor Emeritus in 1927, although he continued to hold clinics and to lecture to the senior class up to the time of his death.

Dr. McClanahan was an ex-Vice-President and Chairman of the Section on Diseases of Children of the American Medical Association, a member of the American Pediatric Society, the American Society for Study and Prevention of Infant Mortality, the American Teachers of Diseases of Children (President, 1914-15), Nebraska State Medical Society (President, 1901), Douglas County Medical Society (President, 1912), and had been a Fellow of the American College of Physicians since 1920. He was also a member of the following fraternities: Phi Delta Theta, Phi Rho Sigma and Alpha Omega Alpha.

Dr. McClanahan's life was a very active one from the time he graduated in medicine; he was always endeavoring to impart the knowledge of his observation and work to others. He was a regular attendant at the meetings of the various national societies, and endeavored throughout his life to keep up with the present trend of medicine. When others took vacations, Dr. McClanahan spent his time at the various clinics of medical societies and abroad to further his education along the lines of advanced science.

Dr. McClanahan's first article "The Practice of Medicine Among the Indians" was published in 1881 in the Medical and Surgical Reporter, Volume 44, Washington, D. C. During succeeding years, he contributed more than fifty articles dealing with pediatric problems in various national journals. His last publication, written in his seventieth year, was a book entitled "Pediatrics for the General Practitioner," published January 1, 1929, by the J. B. Lippincott Co.

Dr. McClanahan's sterling qualities, personality and kindly deeds endeared him to all members of the medical profession as well as to the parents and children whom he had the privilege of having under his care and observation.

—Supplied by Dr. J. A. Henske, Omaha, Nebraska.